ANNUAL REPORT 2005

INTRODUCTION

Following the end of the Twinning Project in October 2004, 2005 was the year of consolidation within the Medicines Authority. The staff of the Authority, after intensive training undergone during the previous sixteen months, embarked on the task of issuing a Marketing Authorisations (MA) for all products that applied for Provisional marketing Authorisation (PMA) under the derogation negotiated in the acquis when Malta joined the European Union in May 2004.

By the end of 2004 all medicines that applied and were eligible were issued with a Provisional Marketing Authorisation. In 2005, with the PMA process completed, the Licencing Directorate started the process of examining the applications in more detail and by the end of the year 347 Marketing Authorisations were issued. This was the first time that a medicinal product was issued with an EU type marketing authorisation in Malta to ensure that medicines available on the local market satisfy EU requirements of quality, safety and efficacy.

Concurrently, the Inspectorate and Enforcement Directorate started carrying out inspections of wholesale dealers and manufacturing premises, while the Post-Licensing Directorate commenced its activities in the various fields that fall within its remit.

Also for the first time the Authority was fully responsible for its own finances. The Ministry of Finance subvention was passed on to and managed by the Authority itself leading to a successful financial audit at the beginning of 2006.

A lot of time and effort was expended on the Quality Management System of the Authority during the year under review The Medicines Authority was assessed as part of the Benchmarking Exercise of national Competent Authorities in November 2005. The audit was successful and the results achieve compare favourably with other more established national agencies.

While on the whole 2005 was a highly successful year for the Medicines Authority, certain issues remain unresolved. Foremost of these is the issue of fees that the Authority should charge for the services it provides to private stakeholders. A proposal for the revision of Legal Notice 372/03 was put forward for consultation in February 2005 and by the end of the year agreement was not yet reached.

The Medicines Authority looks towards 2006 with confidence that it will meet the deadline by when all medicines placed on the Maltese market will, for the first time, be issued with a Marketing Authorisation in line with the stringent criteria set by European Union legislation.

CORPORATE ISSUES

Management Team

Regular meetings of the Management Team were held throughout the year. In total eleven meetings were held and action points followed up between meetings. The Authority also published its first set of audited accounts which covered the period 1st December 2003 to 31st January 2004.

Finance

For the first time, in 2005 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 ended the year 2005 with a deficit of LM3,283 after having to provide for LM29,880 to be refunded to the VAT Department after the Department changed its opinion as to the VAT status of the Medicines Authority.

Fees

In February the Authority embarked on a consultation process to amend Legal Notice 273/03, which regulates the fees the Medicines Authority charges private stakeholders for its services. The review arose since certain activities, mainly carried out by the inspectorate directorate, were not covered by the legal notice. The Authority also took the opportunity to review the whole fee structure to ensure that the fees were equitable for all parties concerned. Particular attention was paid to the scale of fees for variations and the Authority proposed substantial reductions. Consultation meetings were held with Malta Enterprise, The Chamber of Commerce, The Federation of Industry and The Malta Chamber of Small and Medium Enterprises (GRTU). The private stakeholders were very hostile to the proposals put forward by the Medicines Authority and often linked the acceptance of the new fee structure to issues totally unrelated to the Authority. By the end of the year no agreement had been reached.

Quality System

The building of the Quality Management System was maintained. A total of 89 standard operating procedures (SOPs) were finalised and another 26 reviewed. The quality system of the Medicines Authority was audited by three auditors from Finland, Hungary and Cyprus as part of the Benchmarking Exercise of Medicines Agencies (BEMA). The overall rating of the performance was satisfactory and the marks scored (out of five) ranged from 3.5 to 4.5 which compares favourably with other agencies that went through the same benchmarking exercise. Two members of staff of the

Authority were also involved in the benchmarking exercise, participating in the audit of the British, German, Dutch and Estonian agencies.

Human Resources

The freeze on the employment of new staff imposed on the Authority meant that no recruitment was carried out during 2005. This limitation placed a great burden on the administrative staff of the Authority who had to cover those positions that remain vacant. The present staff complement of the Authority consists twenty seven full time employees two part timers, one contract worker and two public officers on loan from the Ministry of Health for a total thirty two employees.

Training

Funds for training under Component 3 of the EU/Malta Twinning Project were available and utilised up to April 2005. These funds were utilised for training employees from the three technical directorates and a member of the Authority's IT Department. Additional funds were made available for training through the UK/Malta Bilateral Collaborative Agreement. These funds were utilised by the Inspectorate Directorate to embark on shadow inspections with their British counterparts in the UK.

Communications

During the year under review, the Medicines Authority launched a new website (www.medicinesauthority.gov.mt) to improve its communications with stakeholders. The website includes information about all activities carried by the Authority as well as guidelines to stakeholders, press releases, circulars, drug safety alerts and links with other relevant sites. The Authority also publishes, via its website, lists of authorised medicinal products and information for the safe use of these products.

The consultation process regarding the publication of the various legal notices was a further means with which to communicate with the private stakeholders. This took a lot of time and effort and although it enabled both sides to understand each other's point of view, the insistence of the organisation to link totally unrelated issues led to a situation were no conclusion was reached by the end of the year.

In May the Office of The Prime Minister set up a Pharmaceutical Working Group to study the impact of the new legislation on the prices and availability of medicines in Malta. The Medicines Authority was represented on this working party by its Chief Executive Officer.

Participation in EU 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 by its CEO and

at the Management Board of EMEA by its Director Corporate Services. Other directors and members of staff attend meetings as explained in the individual directorates' sections later on in this report.

Information Technology

As stated above the Medicines Authority launched its new website during 2005. Besides being more accessible than its predecessor, the new website contains more information and is more user friendly. 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 for a to ensure that the Authority is kept up to date on developments in the IT sector of the European medicines regulatory system.

Other

In 2005 the Medicines Authority signed a Memorandum of Understanding with the Health Division for sharing of information and expertise to support regulatory activities and another one with the Public Health Department for the provision of prosecution services to the Authority.

LEGISLATION

Throughout the year the Medicines Authority was involved in the drafting of legal notices to transpose new EU Directives, mainly Directive 2001/83/EC, Directive 2004/27/EC and Directive 2004/24/EC. The draft legal notices are now awaiting final approval from the Office of the Prime Minister (OPM), which is the department responsible for the vetting of all legal notices. In the interim, Malta has requested a derogation on the data exclusivity period in article 10 and therefore this issue is still being debated. Once this issue of the data exclusivity period extension request is concluded, the Medicines (Marketing Authorisation) Regulations will also be published. This would finalise the transposition of all articles related to the licensing of medicinal products for human use.

Article 126(a) of Directive 2004/27/EC, which had already been transposed during 2004, is planned to be implemented from the beginning of 2006. All documentation, application forms and guidelines have been prepared during 2005 and now published on the Medicines Authority website in preparation for the implementation. The list is also being updated, in conjunction with National Policy and Audit Unit (NMPAU), GPS (Government Pharmaceutical Services) and Department of Health. Once this list is compiled and the fees for the procedure published, it will be made publicly available on the website together with the other documents.

Article 10(1) of Directive 2004/27/EC has been implemented before the coming into force of the Directive, i.e. 30 October 2005. This was done with a view to being able to accept abridged applications, particularly in the Mutual Recognition or Decentralised procedures where the reference product used is not authorised in Malta. In fact, previous to the implementation of this article, the Medicines Authority had to refuse some abridged applications. This article, transposed into the amendment to the Medicines (Marketing Authorisation) Regulations (L.N. 72 of 2005) has been crucial in the issue of abridged applications.

In addition to the above the Authority was also responsible for the publication of LN365/05 (Methadone Rules) and forwarded a draft legal notice to the OPM to regulate dispensing of medical oxygen.

LICENSING DIRECTORATE – ACTIVITIES 2005

Introduction

The Licensing Directorate is one of the main technical divisions within the Medicines Authority and is responsible for the evaluation, assessment and final issue of all licences and authorisations. The key role of the Licensing Directorate is to ensure that products being licensed to be placed on the market are of the required quality, safety and efficacy.

Personnel

The Licensing Directorate this year has seen a decrease of one assessor from its pharmaceutical assessors complement. The case manager, who had left during 2004, has not as yet been replaced. Plans to increase the directorate's human resources to ensure finalisation of the PMA/MA project by the end of 2006 are being finalised with a view to employing more personnel at different levels.

Licensing Procedures

The Licensing Directorate is responsible for the evaluation of several applications including:
National Marketing Authorisations (MA)
Marketing Authorisations via the European systems (MRP, DCP)
Parallel import licences
Clinical trial approvals
Traditional herbal medicinal products registration and homeopathic product registration
Qualified Licences
Paediatric data assessment in the EU worksharing project

Marketing Authorisations

1. National Procedures

(a) PMA/MA Project

As for the previous year, the main workload of the directorate was that of the assessment of applications for marketing authorisation received through the national procedure (PMA/MA Project). By the end of December, 2347 PMA applications had been received and 2228 Provisional Marketing Authorisations (PMAs) issued. 102 applications were refused for various reasons, but mainly on lack of evidence that the product is authorised in other Member States or necessary documentation not having been provided by the applicant.

As the dossiers started to be submitted, Phase II of the assessment process started at the end of 2004 and picked up slowly during 2005. By December, 347 MAs had been issued, most during the last 6 months. Currently, 500 applications are in process, 100 are halted because some form of documentation is being requested from the applicant, and those pending validation are around 655. Approximately 420 dossiers are still to be received and we have received confirmation from the Marketing Authorisation holders of 125 products for which a dossier will not be submitted, and for which therefore, assessment will not proceed and a marketing authorisation cannot be issued.

Provisional Marketing Authorisations

	Jan	**Feb**	**Mar**	**Apr**	**May**	**Jun**	**Jul**	**Aug**	**Sep**	**Oct**	**Nov**	**Dec**
App Received	14	10	0	1	5	9	1	3	4	4	5	0
Issued to date	2153	2176	2191	2191	2194	2197	2203	2209	2218	2220	2228	2228
Work in Progress	39	30	23	20	22	28	23	24	18	19	17	16

Table 1 *PMA/MA applications received, in progress and PMAs issued in 2005*

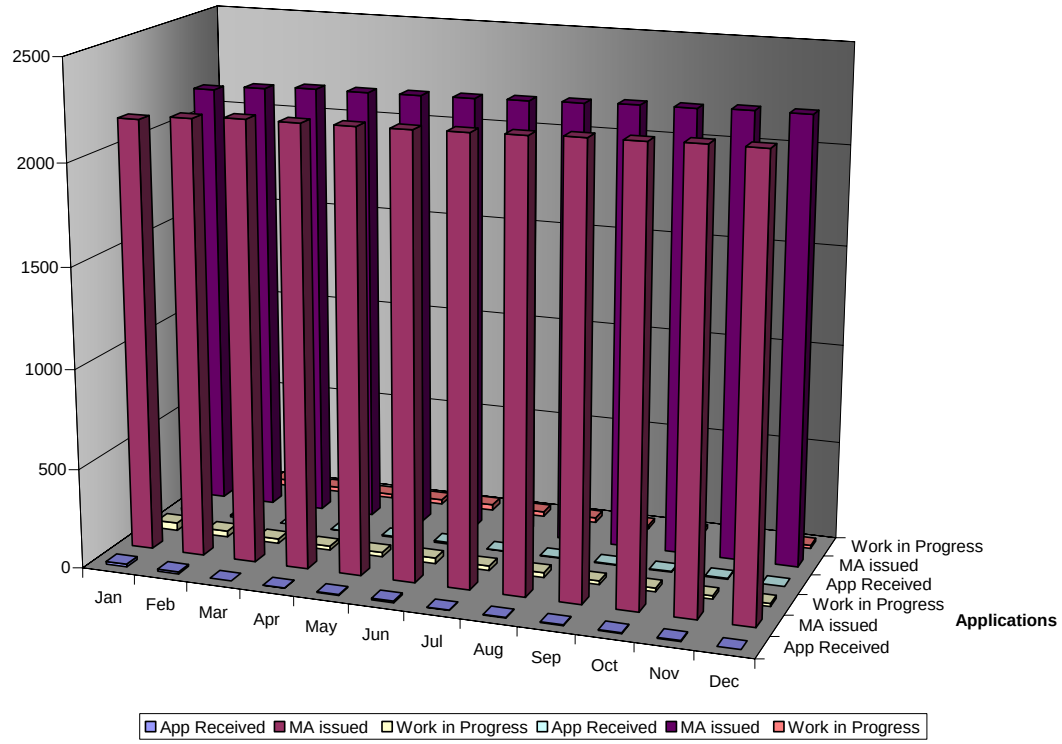


Chart 1 *PMA/MA applications received and PMAs issued in 2005*

Marketing Authorisations

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Issued to date	0	0	0	0	0	0	32	74	74	193	270	325
Work in Progress	2	2	3	3	9	9	9	10	12	11	21	22

Table 1 *Marketing Authorisations in progress and issued to date (2005)*

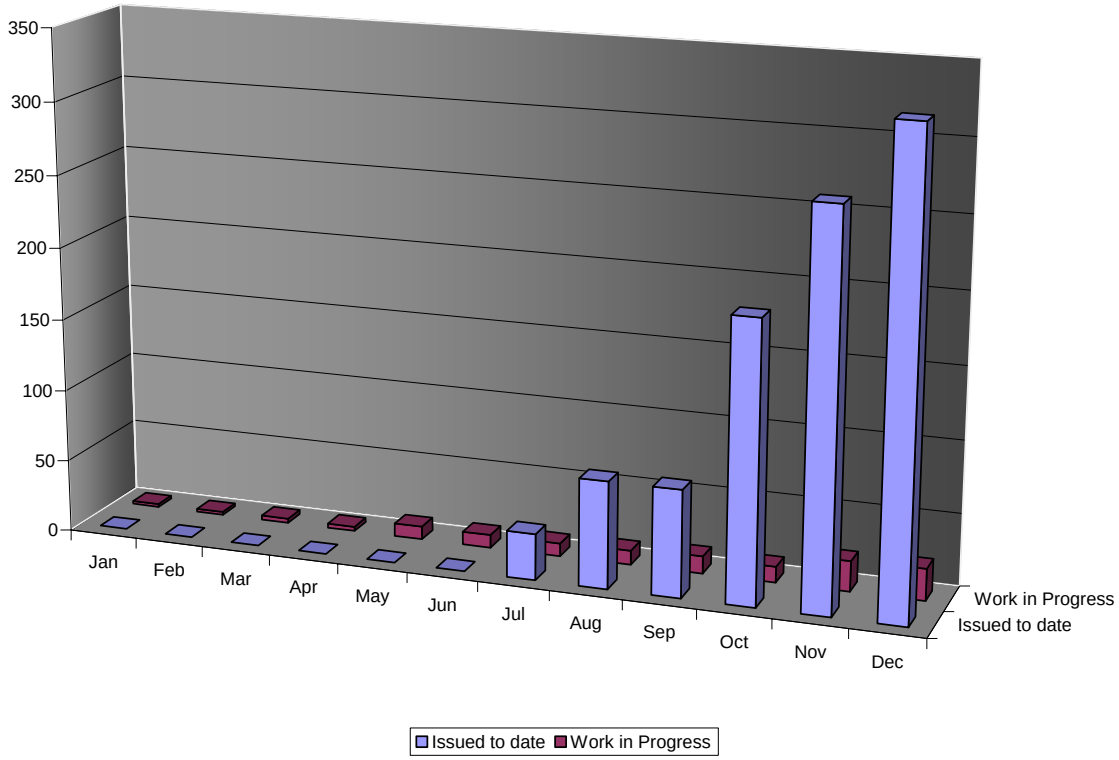


Chart 2 *Marketing Authorisations in progress and issued to date (2005)*

(b) New national applications

One national application was assessed and a marketing authorisation issued in 2005. National line extensions are also being processed. Twenty two (22) applications have been received so far and marketing authorisations issued for three products.

2. European Procedures

(a) Mutual Recognition Procedure (MRP) Applications

The number of applications for products received through the Mutual Recognition Procedure and the new Decentralised Procedure can be seen in Table 3. The CTS tracking system is crucial in communicating with the Reference Member State (RMS) and the other CMSs involved in the MRP, and establishing the critical time-lines of the particular MRP and the progress in the validation and assessment of the applications by the other CMSs.

	Jan	**Feb**	**Mar**	**Apr**	**May**	**Jun**	**Jul**	**Aug**	**Sep**	**Oct**	**Nov**	**Dec**
App Received	11	4	12	16	3	24	5	8	7	12	5	1
Issued to Date	0	0	0	0	0	8	8	17	17	35	54	57
Work in Progress	34	76	69	84	84	102	103	107	111	105	94	92

Table 3 *Applications received through the MRP, work in progress and issued (2005)*

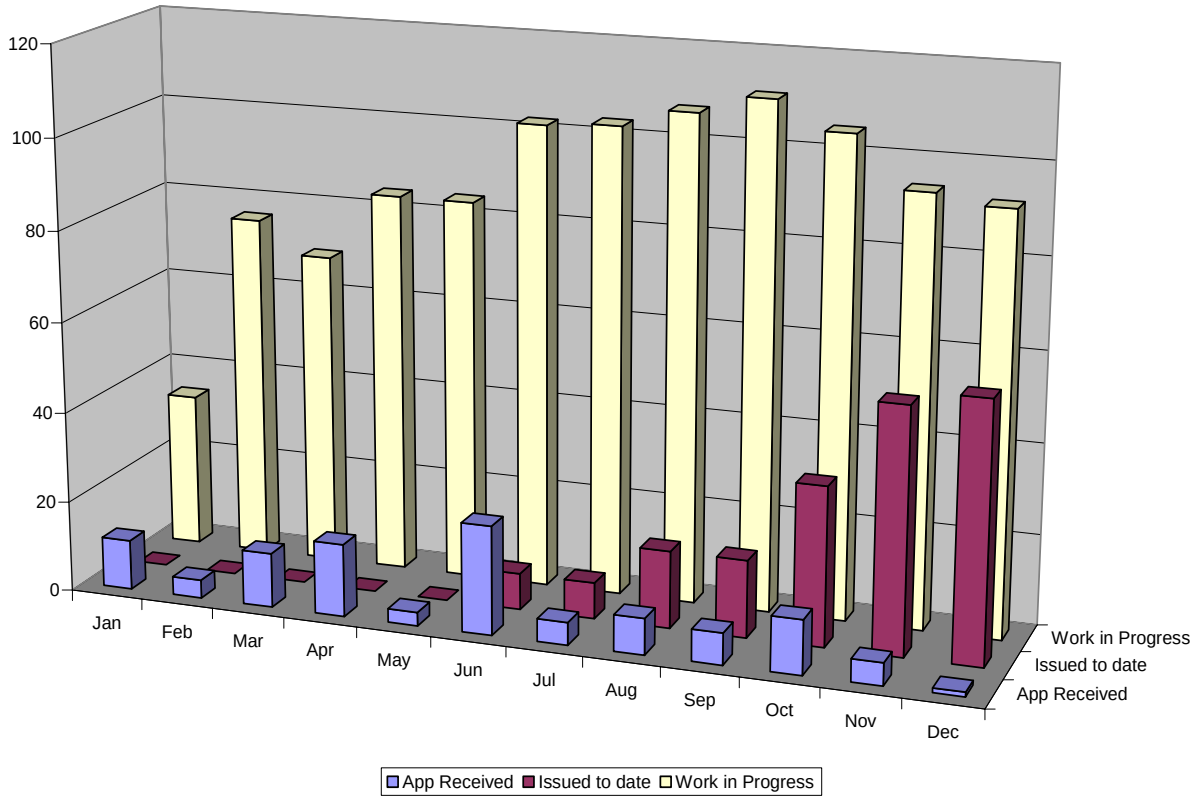


Chart 3 *Applications received through the MRP, work in progress and issued (2005)*

(b) Decentralised Procedure (DCP) Applications

The first application for a marketing authorisation received through the Decentralised Procedure was received in November and is currently being processed.

Malta as Reference Member State and the impact on the Licensing Directorate

The impact of the involvement of Malta as a Reference Member State is being examined in terms of human resources and additional technical training in conjunction with the other directorates. A policy decision needs to be taken with regards to the remit of the authority in relation to processing national applications with a view to acting as Reference Member State. If this plan is to be followed, recruitment of staff with the necessary experience will be necessary in the short term with medium to long term plans of training the technical people already employed by the Medicines Authority and complementing the resources present with others in different areas.

3. Parallel Importation applications

Following the publication of the legislation regulating parallel imports late in 2004, 42 applications have been received by the end of 2005 which have all been successfully processed and 42 parallel import licences issued within the timeframes.

4. Clinical Trials

To conduct a clinical trial locally, one must submit applications with both the Medicines Authority and Ethics Committee and an authorization by the Medicines Authority and a separate positive opinion by the Ethics Committee are required.

During 2005 the Medicines Authority received 2 applications from commercial sponsors to conduct clinical trials in Malta. One trial was authorised by the Medicines Authority and the other trial was withdrawn by the sponsor during the assessment period.

5. Traditional Herbal Medicinal Products and Homeopathic products

The THMP (Traditional Herbal Medicinal Product) transition list now includes another 79 products in addition to the 450 products which may be eligible for simplified registration within the 7 years derogation that is stipulated by the legislation for herbal medicinal products to come in line. No applications for a marketing authorisation of a herbal medicinal product through the simplified registration procedure allowed for by Directive 2004/24/EC have been received.
The expertise required for the assessment of these products needs to be built up as no specific training on this area has been given. The problem being encountered is when an applicant would like to place a new herbal medicinal product on the local market, particularly where the product is not yet registered in another Member State. The registration procedure, both from the administrative and the technical perspective needs to be implemented by the Authority to be able to fulfil its obligations toward stakeholders in the registration of such products, which at the moment cannot be carried out.

6. Qualified Licences

The set up of the system for the implementation of article 126(a) of Directive 2004/27/EC has been finalised following the publication of the legal notice late in 2004. All the application forms and guidelines are accessible on our website and the fees for this procedure, once approved, will also be published in the beginning of the year. The necessary administrative procedures, including the creation of a data base, are all in place. No applications have as yet been received.

7. Paediatric data assessment

Malta was involved as “concerned member state” in the assessment of data within the European work-sharing paediatric data assessment exercise being carried out through MRFG/CMD. Malta was involved in the assessment of 14 products during the first wave of assessments. Malta has also volunteered to act as co-rapporteur in the assessment of a product during 2006.

Borderline Classification Committee (B.C.C)

During 2005 the Borderline Classification Committee held twelve meetings in total. Furthermore, the committee also held meetings with other bodies throughout the year. These included:
a meeting with Malta Standards Authority (MSA) to discuss gaps and overlaps in certain procedures of both organizations and also to discuss particular groups of products and certain individual products.
a meeting with Plant Health Department and MSA mainly to discuss disinfectants and biocides and
a meeting with the Food Safety Commission and MSA to discuss the Food Supplement Regulations and Herbal and Homeopathic medicinal products.

Products were referred to the BCC from the Malta Standards Authority (MSA), the Government Pharmaceutical Services (GPS), from pharmaceutical companies both local and abroad, and from Competent Authorities in other Member States.

A total of 335 products were reviewed by the BCC during 2005. A decision on classification was taken on 285 products, 63 classified as medicinal products, 180 classified as non medicinal products, and 42 were included in the traditional herbal medicinal products list which would benefit from the simplified registration scheme.

The other 50 products contained the ingredient ‘glucosamine’ which is currently being discussed at EU level. Applicants, in view of the fact of the safety of the product, were officially informed of the situation and, as soon as the outcome at EU level is finalized, the applicants will be informed accordingly on the way forward for these products.

Another 13 products submitted during 2005 are pending due to various reasons, such as awaiting requests for further information on the products from other Competent Authorities in other Member States or from applicants, awaiting finalization of particular EC Directives, such as the Biocide Directive, or further discussions with other organizations are necessary, such as those regarding the level of vitamins that will be permitted in food supplements.

During 2005 an applicant appealed to a decision taken by the BCC on one product. This was forwarded to the Appeals Committee of the Medicines Authority. The latter agreed with the decision of the BCC and the applicant was informed accordingly.

The BCC also consults with other entities both locally and abroad in order to obtain the opinion of experts in other areas. During 2005 five (5) products were discussed with the MSA and three (3) products were discussed with MSA and Plant Health Department. A number of products were also referred to the UK Competent Authority for their opinion.

In order to achieve more transparency, the BCC publishes a list of products that were classified as medicinal products. This list was uploaded on the website of the Medicines Authority under the section ‘Borderline Products’.

When referring a product for classification applicants were encouraged to make use of the application form which is available on the website of the Medicines Authority and on the premises. The aim is to obtain as much information as possible on the product and to standardise the procedure to be followed.

The BCC plans to meet more often due to the increase in the number of products that are referred for classification. It also plans to have an official time-table for meetings such that applicants would know when to expect a reply following discussion of their product.

Information Made Available Publicly

In line with Directive 2001/83/EC as amended and with the policy of making information accessible to the public in general and to stakeholders and health care professionals, all licences issued are published on the Medicines Authority website. The lists of all marketing authorisations and licences issued by the directorate are published and updated monthly. This includes lists of PMA, MA and parallel import licences. The final approved Summary of Product Characteristics (SPC) and package leaflet (PL) of each authorised product are also published.
The licensing section of the Medicines Authority website has also been updated to reflect any changes in implementation and more information has been included.

Linguistic Check Process of Centrally Authorised Products Information

This process is currently on hold, as most Marketing Authorisation holders are not submitting Maltese translations of the Commission decisions on Centrally Authorised products. However, the Medicines Authority has to prepare short term plans, if the derogation on the use of the Maltese language ends in May 2007, the increased work-load for the checking of translations will have to be addressed.

Participation at Meetings, Working Parties and Conferences

Members of the licensing section participated actively in the European medicines regulatory system through their involvement in many committees, working parties and conferences.

Meetings and working parties attended regularly by Licensing Staff at the European Medicines Agency (EMEA) include the Mutual Recognition Facilitation Group (MRFG) (which has now changed to the Co-ordination Group for the Mutual Recognition and Decentralised Procedures, as per Directive 2004/27/EC), 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.

Other important European Presidency meetings attended include EMACOLEX, Pharmaceutical Committee meetings, Meetings for Competent Authorities on Homeopathic Medicinal Products.

As per current policy, meetings attended are those that are strictly mandatory or deemed necessary by management. However, some meetings, such as those related to homeopathic products, Notice to Applicants (where pharmaceutical directives and regulations are interpreted to prepare guidelines for applicants) should also be attended, even if these are not reimbursed. These meetings are important to the Medicines Authority particularly if the remit of the Authority is expanded to include that of being a Reference Member State. The staff would need much more expertise both in the regulatory and the technical fields to be able to deal with such applications, particularly in the Licensing directorate.

Conclusion

The review process carried out on products on the market as part of the PMA/MA project has remained the focus of the Licensing Directorate during the year 2005, although all assessors are also involved in the variations that are being received both via the national and the European procedures. The impending deadline of December 2006 has meant that new projects had to take secondary priority. It is important that the Marketing Authorisations for valid applications for products on the market are finalised by the end of 2006 and to this end the Licensing directorate will be able to increase its human resources to be able to carry out its obligations in this respect. Many companies have asked for extensions for dossier submission, some even up to June 2006, and this will set the department back on its plans if these dossiers do not arrive on time. Resources have been planned to be able to finalise all assessments by September 2006. If the necessary documentation is not received in time for this to be possible, the marketing authorisations for some products may not be issued by the deadline. It is planned that all products for which documentation has been received are all given feedback on the review process by September, such that positive feedback from the companies would mean that marketing authorisations can be issued by the deadline.

All the legislation relating to licensing activities that had to be amended following the review of the legislation has been completed. Implementation of the legislation for herbal and homeopathic medicinal products is being carried out. New national line extension applications are still being processed as much as is possible to allow these products (already licensed in other EU/EEA member states) on the market as early as possible. Malta is still participating as CMS in the Mutual Recognition Procedure and the new Decentralised procedure, and also in the EU worksharing project of paediatric data assessment. The focus in the coming year will have to take into account other procedures, and planning the necessary resources for the department with a view to being technically and administratively able to carry out other procedures, such as the registration of herbal and homeopathic products and more importantly, being able to act as Reference Member State in the MRP and DCP once the necessary resources and training are made available. It will be important to identify the needs of the department for these activities during the year 2006 such as to be able to plan the necessary training and resources to be able to be functional in 2007.

INSPECTORATE AND ENFORCEMENT DIRECTORATE – ACTIVITIES 2005

Introduction

The Inspectorate and Enforcement Directorate is responsible for the inspection and licensing of all pharmaceutical activities within the Maltese territory. The Directorate is also charged with the remit to enforce Legislation pertaining to medicinal products for human use.

The Directorate additionally strives to introduce and maintain pharmaceutical standards in various areas, such as Good Manufacturing Practice and Good Distribution Practice in accordance with the extensive EU legislation that governs pharmaceutical products. In order to fulfill these obligations the Directorate has fully integrated within the EU system and actively participates and contributes within the proceedings of the European Medicines Agency (EMEA).

Remit of the Directorate

As detailed in the Medicines Act 2003 and following the process described above the remit and responsibilities of the Directorate have been identified as consisting of the:

- inspection and licensing of the manufacture of Medicinal Products for human use as well as Active Pharmaceutical Ingredients (API).
- inspection and licensing of the distribution and sale of medicinal products for human use.
- inspection and licensing of public and retail pharmacies.
- inspection of Clinical Trial sites
- certification for export and issue of Certificates of Pharmaceutical Products (CPP`s) and GMP certificates for locally manufactured medicinal products.
- management of drug alerts and batch recalls.
- enforcement of standards and compliance with the Medicines Act 2003.
- provision of advice to the Licensing Authority in relation to pharmaceutical activities.
- establishment of a good communications strategy with the relevant stakeholders.

Personnel

The personnel of the Directorate remained stable in 2005 and consisted of a Director, five inspectors, who also perform duties as enforcement officers, and an administration clerk.

Legislation

An extensive revision of the Medicines Act and the various Legal Notices was undertaken in view of the European review of pharmaceutical legislation and the publication of new Directives. A new system of consulting and discussing the legislation with the relevant stakeholders was introduced. This procedure resulted in longer timeframes for the publication of the new legislation. The following legislation has been reviewed and amended:
Medicines Act 2003 – the final draft has not been published as all Acts that have been amended will need to be approved by Parliament within the framework of an Omnibus Act.
L.N. 143 of 2004 - Manufacture of Medicinal Products for Human Use Regulations has been amended to also include importation activities and has been published as L.N. 381 of 2005.
L.N. 154 of 2004 – Importation and Wholesale Distribution of Medicinal Products Regulations has been amended as L.N. 386 of 2005 and presently include wholesale dealing activities only.

The legal notices under point 2 and 3 transposed the relevant sections of Directive 2001/83 EC as amended Directive 2004/27 EC.

A new Legal Notice concerning Clinical Trials has also been published and the inspectorate gave the necessary input regarding the relevant aspects of manufacture and importation. The same input was given as regards the publication of a L.N. that transposes the ratification of the European Pharmacopoeia Convention.

Another Legal Notice which was within the responsibility of the Directorate is the revision regarding the Prescribing and Dispensing of Methadone. Following extensive discussions and consultations this rule was published as Legal Notice 365/05 on the 4th of November. A new Legal Notice for the authorization of dispensing of medicinal oxygen from premises other than a pharmacy has additionally been drafted following extensive consultations with the stakeholders involved. This Legal Notice (L.N. 398 of 2005) was issued in accordance with the provisions of article 79(2) of the Medicines Act 2003 and is expected to have a very positive impact on the provision of oxygen to patients.

Additionally a Legal Notice which required considerable effort and extensive consultation was that regarding the fees to be paid for the services offered by the Medicines Authority. This legislation is crucial to the Authority and especially to the inspectorate since no fees for the inspection services have ever been approved and published. The fees for the pharmaceutical activities have not been approved as yet.

The Inspectorate was also involved in the process of submitting feedback and its expertise in a number of European Regulations and Directives that are in the process of being published, such as the Regulation that will amend the EMEA fees, the Directive on compulsory licences and those about patents and consumer protection cooperation.

EU Obligations

European Medicines Agency (EMEA)

The Inspectorate has fully participated in the EMEA meetings pertaining to GMP and GCP through the Director who is the nominated delegate for these meetings. All meetings, which total to eight, have been attended.

European Medicines Enforcement Officers (EMEO)

The Director Inspectorate has also attended the meetings of the EMEO in 2005 and participated actively in this forum by giving presentations and chairing of workshops. Two meeting were held, one in Dublin and the other in London.

The remit of the group 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.

Through participation in this forum the Medicines Authority has been given access to a new database, Integris. This is a project of the EU Commission and is a highly secure, role-based authenticated web application for the sharing of historic and current data between law enforcement agencies and regulatory authorities. This database will serve as a good tool to obtain timely information and to share and network with other member states.

European Pharmacopoeia

A medicines inspectors who has been nominated as delegate for the European Pharmacopoeia attended the 121st session that was held in March. This was the first time that Malta participated as a full member.

MRA audit

Following the successful pre-MRA audit that was held between the 18th and 25th of October 2004, the Inspectorate is expecting that the Canadian audit will be carried out in 2005. All the deficiencies identified have been acted upon.

Internal Audit

All the issues raised during the internal audit that was carried out October 2004 have been addressed and there are no pending issues.

European Joint Audit Program

During the coming year a process will be initiated within the EU whereby all Inspectorates of each Competent Authority will have to be audited by other member

states for compliance with the Quality System and EU standards. The Medicines Authority will not be within the first group of countries to be audited in view of the successful pre-MRA audit that was held in 2004.

Inspections and Issuing of Licenses

Manufacturing Authorisations

During 2005 four manufacturing authorizations were renewed and these were issued in the new EU format as established in the Compilation of Community Procedures. GMP certificates were issued for the first time for these sites. A follow up inspection was necessary for one of the companies but when re-inspected the company had addressed all the deficiencies and issues.

A new application for a repackaging site was received in 2005. The inspection has been finalized and the Medicines Authority is awaiting the reply regarding the corrective actions from the company.

A very high activity in the area of GMP is expected during 2006 as the number of companies will more than double.

Variations

Two applications for variation of a manufacturer's licence were processed and new licenses issued within the stipulated time frame of 30 days.

Export Certificates

36 export certificates were issued to a local manufacturing company. 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.

Import Authorisations

Currently there are three pending applications for an import licence from applicants in possession of a wholesale dealer's licence. These will be inspected according to the EU GMP standards during 2006 for the purpose of issuing the importing licence.

Wholesale Dealing Authorisations

All the wholesalers that had to be inspected in 2005 have been visited and the inspection programme for 2006 was also initiated. In fact 47 wholesalers have been inspected. Three new applications for wholesale dealing were received and these have been processed satisfactorily and the licences issued. The renewal licences for the other 44 sites have not been issued in view of the fact that the fees for the inspection activities have not as yet been approved. It is planned that once the fees are approved the licences in the new EU format will be issued for these sites. 14 companies have

decided to drop their licence and not proceed for renewal. Two of these were because of merging of companies.

Suspension of Licence

One wholesale dealer's licence was suspended for a period of one week following adverse inspection findings during the renewal of licence. Complaints had already been received in relation to this company and action was taken to bring forward the inspection in order to verify the allegations. Following the suspension the company has been quite cooperative and has been following our recommendations accordingly.

Revocation of licence

One wholesale dealer's licence was revoked following the placing on the market of a product without a marketing authorization and dealing in parallel importation without the necessary licences in place. Although the company was given the opportunity to comply further violation of legislation and standards were identified during the recall process and this led to an immediate revocation of the licence.

Variations

One wholesale dealer's licence was varied at the request of the licence holder.

Pharmacies

The Inspectorate took the full responsibility for inspection of pharmacies as from January 2005. As of January next year the Medicines Authority will also be responsible for the pharmacy roster. In fact the roster for the first quarter of 2006 has already been worked out and issued.
Issues relating to new permits and pending applications for new pharmacies will still be managed jointly with the Public Health Department until definite policy decisions are taken by the Ministry of Health and standards established in this respect.

Process verbal

A number of 206 inspections at retail pharmacies were carried out for the scope of performing 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. A proactive approach was taken to introduce additional standards relating to temperature control and monitoring and pest control.

Pharmacy Spot Checks

20 spot checks were carried out on pharmacies. These were initiated following reports and/or complaints from other Departments, stakeholders or the general public.

Sampling of Medicines

Following the established of a contract with a foreign lab for the analysis of medicines in mid- 2005 the sampling project was initiated and the sampling plan established for the year was covered. 8 different products were analysed and all of these passed the tests and were found to be up to standards and specifications.

Enforcement

23 complaints were received and all of these were investigated. 19 cases lead to an enforcement action. All cases, except 2, have been closed. 1 case was referred to the police and the Medicines Authority has provided its supporting the investigations. The most common breaches were those relating to the unauthorized placing of parallel imported products on the market.

Court cases

The Medicines Inspectors provided their services as witnesses in 16 court cases for prosecution proceedings initiated against offenders. Most of these had been initiated months ago prior to the establishment of the Medicines Authority and new systems.

Other Activities

Inspection Review Group

3 meetings of the Inspection Review Group have been held in relation to 4 cases. The remit of this group is to consider action in cases of critical deficiencies and serious non-compliance.

Batch Defect Reports

During this year the Inspectorate received and processed 55 reports of quality defects. 51 reports were received from foreign and 4 from local sources. 4 batch recalls were effected following these reports and 1 caution is use notice was issued.

No batch recalls were initiated or reported by local manufacturing companies in respect of the products within their portfolio.

In addition the necessary steps were taken to remove and instruct wholesalers to collect 7 products from the market following investigations.

Qualified Persons` Assessment

QP interviews were held in April. 8 applications were received and the applicants were interviewed by a panel from the Medicines Authority. 5 applicants were successful, 2 under the permanent provision and three under the ‘grandfather’

provision. This was the last opportunity for applicants to apply for the 'grandfather' status under article 10(1) of LN 143/04.

Seminars

To fulfill the Inspectorate's objective to initiate and put in place an effective communications strategy with the various stakeholders a seminar was held in April in collaboration with the Malta Qualified Persons Association. The topic covered related to the Microbial Limit Tests for Non-sterile Dosage Forms.

Meetings

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 Inspectorate 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.

NEW INITIATIVES

Pharmaceutical Inspection Convention Scheme (PICS)

The Director Inspectorate has attended for the first time an event organized by PICS, the annual seminar that was held in September in Romania. The topic covered packaging operations. The aim for this participation was to acquire more information on PICS and the process to achieve membership. A report and case for membership have been prepared and presented to the CEO and Health Division. This report highlights the advantages, responsibilities and obligations of becoming full PICS members.

It is perceived that participation in PICS would greatly increase the exposure of the Medicines Inspectors to GMP issues and would provide for ongoing training. It would also send a signal to other competent authorities that the Maltese Inspectorate is committed towards sustaining the standards achieved and that continual improvement will be emphasised.

Training

Due to the limited amount of funding the inspectors were not able to fulfill the requirement of a minimum of 10 days training. However some training, mainly in the area of GCP, was provided through shadow inspections, seminars, and training sessions organized by the EMEA and EDQM. It is the intention to provide more training opportunities for inspectors in the coming year.

Conclusion

The operations within the directorate are now in full swing and a lot of achievements have been made during 2005. It is expected that this high level of activity will have to be sustained during the forthcoming year since it is already established that 7 new manufacturing companies (1 API, 2 full manufacturing, and 4 repackaging) will be opening in 2006. This augurs well for the Medicines Authority and for Malta.

In the context of the track record delivered in the past months the Inspectorate Directorate looks forward to the coming year with optimism and will strive to fully achieve its objectives and the safeguard of public health.

POST -LICENSING DIRECTORATE ACTIVITIES 2005

Introduction

The Post-Licensing Directorate is a Technical Directorate within the Medicines Authority that is responsible for all activities related to the post-marketing phase of medicinal products for human use. These activities include pharmacovigilance, haemovigilance, processing of variations to marketing authorisations, as well as the regulation of promotional material on medicinal products for human use. In order to fulfil these obligations the Directorate has fully integrated within the EU system and actively participates and contributes within the proceedings of the European Medicines Agency (EMEA).

Post-Accession

The overall objective in 2005 following the completion of the twinning project was to be responsible for the implementation and enforcement of relevant legislation with respect to the regulation of medicinal products for human use and pharmaceutical activities.

Structures and working methods of the Pharmacovigilance Section were established and reinforced. The systems developed throughout 2004 to facilitate compliance on the part of the Pharmaceutical Industry and increase Adverse Drug Reaction (ADR) reporting by Healthcare Professionals were in production and monitoring techniques through internal and external audits (The Commision's "An assessment of the European Community System of Pharmacovigilance" and "Benchmarking the management systems of the European competent authorities to assure the quality of the authorisation and supervision of medicines of human and veterinary use") have been carried out. An IT infrastructure in order to comply with the obligations set out in EC Regulation 726/2004 and Directive 2001/83/EC as amended, with respect to the electronic transmission of Individual Case Summary Reports has been set up and productivity achieved.

The external Audit of the Pharmacovigilance system in Malta was carried out by a Fraunhofer-Institute Systems and Innovation Research (Breslauer Str. 48, 76139 Karlsruhe, Germany) official in May 2005 over 1 visit. During the visit, the various issues essential for the compliance of the Pharmacovigilance Section that respects and fulfils the EU criteria were identified and examined. The results of this audit will form part of the Commission's Report "An assessment of the European Community System of Pharmacovigilance". Work in 2005 also focused on finalising the following legislation: the amendments of the Medicines Act (2003), the new Legal Notice of 2005 on Pharmacovigilance, and Legal Notice 380 of 2005 "Medicinal Products (Advertising) Regulations". These regulations effectively transpose Directive 2004/27/EC amending Directive 2001/83/EC.

Personnel

The staff of the Post-Licensing Directorate throughout 2005, were three quality assessors, 2 medical assessors and a Post-Licensing Director. An administrator has been allocated to assist the Directorate in the day to day operations and management. The quality assessors have fully integrated within the Department and have gained a considerable amount of knowledge and experience throughout this year when carrying out their duties. It is imperative now, that quality assessors undergo ongoing training and participate in committees of the EMEA related to Post-Licensing issues in order to obtain a wealth of knowledge and experience in those activities that are considered as innovative to the local scenario and for those areas that will be covered by upcoming new EU legislation.

EU participation and the EMEA

Throughout 2005, the Directorate has taken the necessary steps to become fully integrated and participate within the proceedings of the EMEA. Members from the Medicines Authority nominated as the Maltese delegates, attend and participate in meetings of the Committee for Medicinal Products for Human Use, the Pharmacovigilance Working Party, the Joint Implementation Group, the Safety Working Party and the Working Party on Pharmaceuticals and Medical Devices. These meetings are fully reimbursed and were attended on a regular basis. In 2005, the following meetings were attended by staff of the Post-Licensing Directorate:

Meeting	**Number of meetings attended in 2005**
Committee for Medicinal Products for Human Use	11
Pharmacovigilance Working Party	11
Joint Implementation Group	2
Working Party on Pharmaceuticals and Medical Devices	9

Quality Management System

Besides being audited by the BEMA exercise, in May 2005 the Post-Licensing Directorate got audited by Fraunhofer-Institute Systems and Innovation Research (Breslauer Str. 48, 76139 Karlsruhe, Germany) with respect to the Commission's pan European Audit of the Pharmacovigilance system in Malta. The general aim of the project was to analyse how the European Commission's European Medicines Agency, EU Member States' medicines agencies, marketing authorisation holders (MAHs) collaborate in the surveillance of adverse effects of medicinal products. One objective of this project was to put forward recommendations to make the system more robust.

The Fraunhofer visit took place on 18 May 2005. The interview and a written survey were carried out with the Post-Licensing Director and a Quality Assessor from the Post-Licensing Directorate. The main topics of the interview included questions

related to process activities (especially data collection, data management, quality control/quality assurance, safety signal detection, safety issue assessment, decision making process, action plans to protect public health, communication process with stakeholders, quality assurance), the relevant stakeholders and questions with respect to the resource availabilities/functional capabilities of these stakeholders.

The final report aims to give an overall summary of the European pharmacovigilance systems as a whole, not on the systems on each individual Member State. Yet, in the final draft of the report issued on 16 December 2005, Malta, together with Estonia and Hungary were singled out for praise for their efforts in data collection, in contrast with other new Member States were there is still much criticism in their self-assessments (Fraunhofer-Institute Systems and Innovation Research, "*the Assessment of the European Community System of Pharmacovigilance"*. DEC 05, 1-177.)

Legislation

During the first quarter of 2005, the Post-Licensing Directorate participated in the drafting of regulations on new Legal Notice of 2005 (Pharmacovigilance Regulation) and Legal Notice 380 of 2005 "Medicinal Products (Advertising) Regulations". These mainly transpose Directive 2004/27/EC and came into force on 30 October 2005. The Directorate held several internal discussions on the legal and operational impact of the Regulations and analysed proposals and recommendations from various professional bodies. Furthermore, since these Legal Notices introduce new obligations on applicants for marketing authorisations, wholesale dealers and manufacturers external consultations with stakeholders during the 2nd and 3rd Quarters of 2005 were carried out.

Activities of the Post-Licensing Directorate in 2005

Variations to Marketing Authorisations

Number and type of variations to marketing authorisations processed in 2005:

Procedure	**Number**
National Applications	55
Mutual Recognition Procedure	172
Type of variation	**Number**
Type IA	91
Type IB	66
Type II	71

Pharmacovigilance activity

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

In 2005, pharmacovigilance activity consisted of management of the following drug safety reports/requests:

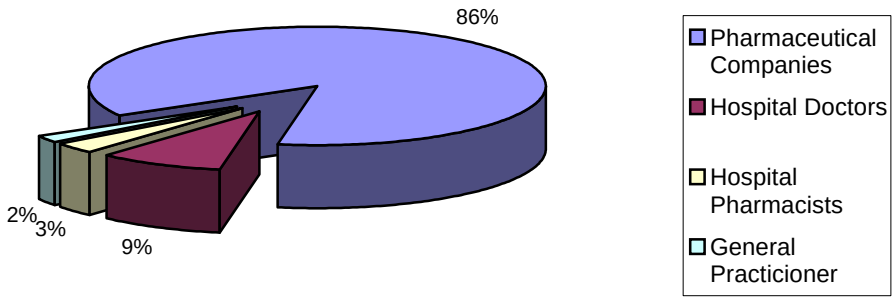
13 were Individual Case Safety Reports (ICSRs) from healthcare professionals in Malta,
55 CIOMS forms of Adverse Drug Reactions ADRs occurring locally forwarded by industry
49 Non-Urgent Information Requests
20 Rapid Alerts
93,360 CIOMS forms of ADRs originating in third countries

Measures taken to encourage ADR reporting by practicing healthcare professionals included the introduction of the self addressed ADR reporting form; the publishing of the second issue of the Drug Safety Bulletin. Circular No DH 70/05 was issued to promote and educate health care professionals with current licensing and post-marketing activities and obligations introduced by the transposition of Directive 2001/83/EC in the Maltese Legislation.

Source of Data

Analysis of the ADRs received showed that the pharmaceutical industry is responsible for most ADR reports submitted in 2005 to the MA (figure 1). Healthcare professionals (doctors and pharmacists) also submitted ADR reports to the MA. It is expected that with increased awareness amongst healthcare professionals, the reporting rate is expected to increase.

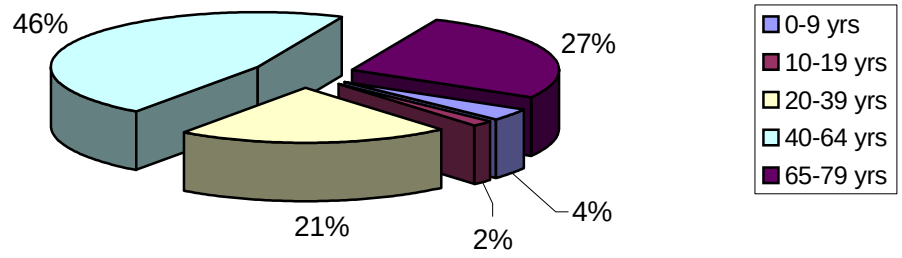
Figure 1: Maltese ADR reports for 2005 according to source of data



Age of Patient

Analysis of ADRs by age of patient (figure 2), showed that the most common patient age group that ADRs are reported is between 40 to 64 years (*n*= 26), followed by 65 to 79 years (*n*= 17) and 20 to 39 years (*n*= 6).

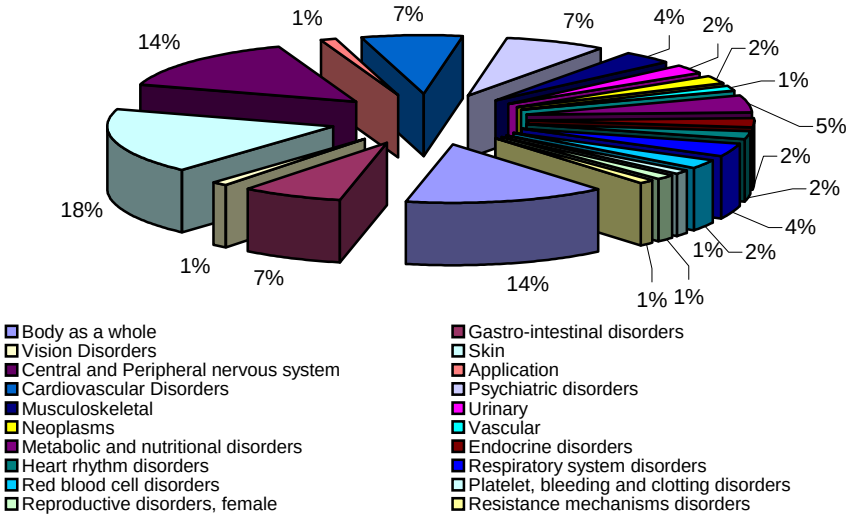
Figure 2: Maltese ADR reports for 2005 according to age of the patient



ADRs by Body System

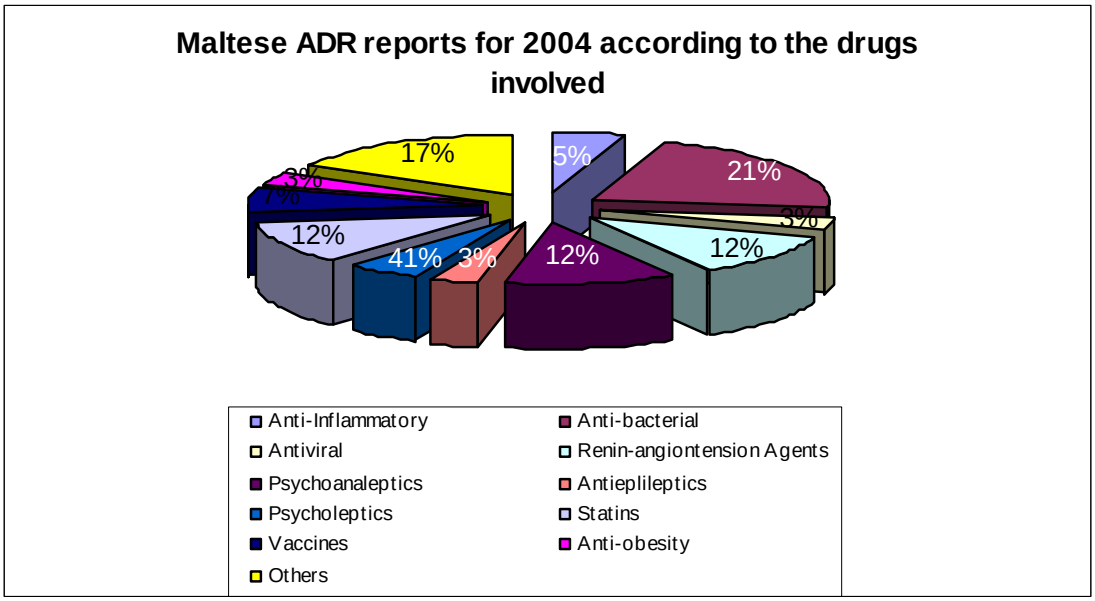
Skin disorders (*n*= 15) is the system-organ class (figure 3) for which ADRs are most reported followed by the body as a whole (*n*=12) and central and peripheral nervous system disorders (*n*=5).

Figure 3: Maltese ADR reports for 2005 according to System-Organ Class



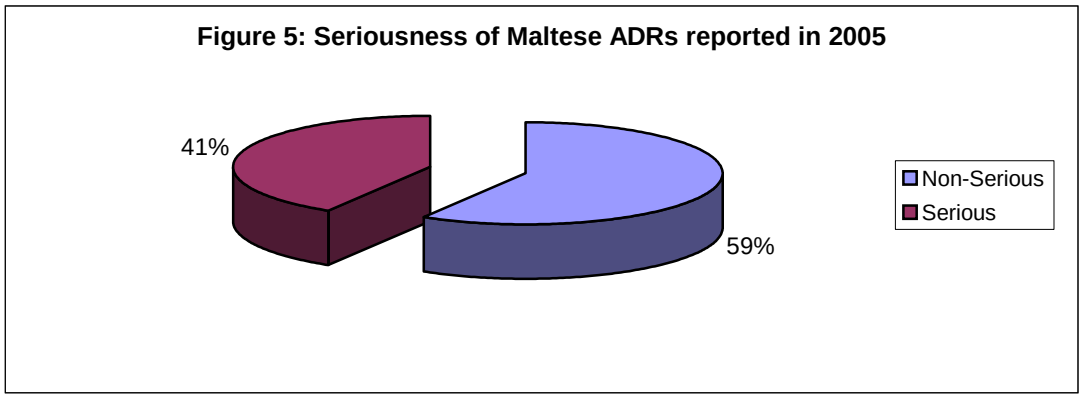
Drugs Involved

The most commonly reported drugs are those used for the alimentary tract and metabolism with the largest number of ADRs being reported for anti-bacterial preparations. psychoanaleptics, anti-thrombotics, renin-angiotensin products, statins, vaccines and anti-depressants being the next most commonly reported drug classes (figure 4).



Seriousness

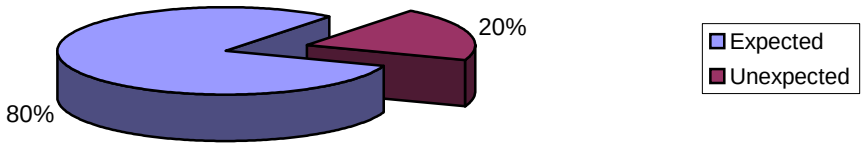
Over half (59%; *n*=58) of the ADRs reported were considered as serious (figure5). The criteria for seriousness included fatal, life threatening, caused or prolonged hospitalisation, caused congenital abnormality, caused disability or incapacity and other medically significant condition.



Expectedness

The majority (80%; *n*=78) of ADRs reported were expected and thus already listed in the summary of product characteristics of the medicinal product (Figure 6).

Figure 6: Expectedness of Maltese ADRs reported in 2005



International Relations

The establishment of the ADR reporting system by the MA and the participation of healthcare professionals, through reporting of ADRs encountered during their practice has not only enabled Malta to comply with existing EU regulations but the transmission of these reports to the WHO Collaborating Centre for International Drug Monitoring, Since 2004, Malta has been a full member.

Regulation of advertising and promotional material

The Medicines Authority has conducted a number of activities relevant to the control of advertising since the setting up of the new system of self-regulation on 1 May 2004. These included:

- Monitoring advertising material
- Investigating complaints about advertising
- Advising industry, health professionals and professional bodies
- Advising the Broadcasting Authority on aired promotional activities
- Guiding the media on publication of articles related to medicinal products
- Enforcement in relation to materials not complying with the Regulations

Over the past year the Directorate handled thirty-seven cases related to advertising which included:

- Addressing 19 formal queries from a variety of sources on implementation of the advertising regulations.
- Investigating and evaluating 9 complaints from stakeholders
- Advising on 9 advertisements forwarded to the Authority prior to publication

Technical matters

A local ADR Database (MDIS) has been maintained in order to record data from locally occurring ADR reactions reported to the MA. Four staff members have also been trained on ADR data input into the European Network, namely the Eudravigilance Web-trader function. Plans for the setting-up of the Eudravigilance Gateway system have been also drawn up and implemented in 2005. Six Joint Implementation Group meetings discussing Eudravigilance implementation were attended in 2005.