MEDICINES AUTHORITY

Introduction

The Medicines Act (Chapter 458) was enacted in March 2003 and was brought into force in November 2003. Thus 2004 was the first year of operation with the Medicines Act in force.

With EU accession on the 1st of May 2004, the Medicines Authority started fulfilling its full remit as a National Competent Authority for the Regulation of medicinal products for human use. The national obligations of licensing activities including registration of medicinal products on the local market, inspection of pharmaceutical activities, enforcement of legislation and post-licensing functions such as pharmacovigilance and adverse drug reaction reporting were strengthened and brought up to the levels required by EU legislation. In 2004 the Medicines Authority assumed the full responsibility for its role in monitoring and enforcement of pharmaceutical activities and of other areas such as advertising.

Capacity and infrastructure

The Medicines Act established the Medicines Authority and during 2004 the organizational structure of the Medicines Authority was built, mainly through the employment of the required personnel. The Chief Executive Officer of the Authority was appointed in March 2004. By the end of the year all the senior management posts as well as the technical and operational posts were filled. The four directorates (Licensing, Inspectorate and Enforcement, Post Licensing and Corporate services) as well as two other departments (Operations and Regulatory Affairs and IT) are in place and operating.

The Twinning project between consortium partners – the Irish Medicines Board (IMB), the Medicines and Health care products Regulatory Agency (MHRA) of the UK and the Medicines Authority in Malta, which was started in March 2003 continued during 2004 and was closed in October of that year; thus lasting for 20 months. The objective of this project was to strengthen the institutional and operational capacity of the Medicines Authority to make it a functional National Competent Authority which could fulfill its national as well as its wide European Union (EU) obligations. Overall the Twinning Project was successful with the main objectives being met in the eight key result areas. 86% of the original workplan in the Covenant was accomplished and all activities were completed within the budgetary framework. The project leader prepared and presented a number of reports highlighting the progress of the project.

Through support from the Twinning Project the Medicines Authority participated in the transposition and implementation of current and new legislation. Extensive preparatory work had to be done prior to the actual process of issue of the various authorisations and licences, and before monitoring activities could start. Each directorate also offered the technical input into the process of consultation with stakeholders, drafting and publication of the legislation subsidiary to the Medicines Act, with a total of twelve legal notices being published in 2004 covering all areas of medicines regulation.

A number of internal technical committees were set up in order to consolidate and strengthen the various decisions that have to take place. These included the Borderline Classification Committee (where individual products are assessed and classified as to whether they are medicinal products), the Parallel Imports Committee, the Mutual Recognition Committee, the Scientific Committee and the Inspectorate Review Group.

The information technology infrastructure was strengthened with installation of the required information systems to enable compliance with EU requirements and participation in activities at the national and EU level. During the second quarter of 2004 various products from the EU-funded call for hardware tender which was a component of the Twinning Project and was issued through the Department of Contracts in 2003 were delivered. A new website for the Medicines Authority started being developed to incorporate the Authority's corporate image and to enable publications of the required information to stakeholders.

Corporate issues

In the absence of the appointment of a director of corporate services up to mid-2004, all the recruitment for the staff of the Medicines Authority in 2004 was carried out by the Foundation for Medical Services on behalf of the Medicines Authority. For the whole of 2004 all financial transactions out of the vote for the Medicines Authority were handled directly by the Ministry of Health. When the Director of Corporate Services was employed, the Corporate Services Department started operating an accounting system and a payroll system and the Medicines Authority started managing its budget and issuing salaries for its employees directly. A budget for 2005 was prepared and the final version was passed for approval by the Ministry for Health and forwarded to the Ministry of Finance.

The Management Team of the Medicines Authority was set up and meetings were chaired by the CEO. The team was extended with the consecutive employment of the different directors and managers reaching its full complement in October. Twelve meetings of the management team were held.

Communication with stakeholders

During 2004, various meetings were carried out with stakeholders, namely the local and foreign representatives of the pharmaceutical industry and leaders of sectional groups and individual companies. In addition to efforts at increasing consultation at the stage of drafting of legislation, guidelines for stakeholders and frequently asked questions documents were placed on the website. Numerous seminars were held covering the different areas of activity to inform those concerned of the procedures and to discuss implementation and legislation.

A common approach is being taken by the Medicines Authority and Malta Enterprise to assist prospective companies. Other meetings are continually being held with wholesale dealers regarding specific issues and the upgrading of standards. Regular meetings with the Parliamentary Secretary in the Ministry of Competitiveness and Communications are also attended. During these meetings the various Government entities present share information about market surveillance and enforcement and aim to reduce bureaucracy and promote investment.

Fees for the various services and licences issued by the Medicines Authority were prepared to be issued for consultation with stakeholders.

EU and International relations and responsibilities

Upon accession the Medicines Authority assumed its full obligations as a National Competent Authority within the European Union. These include active (and in some cases obligatory) participation at meetings of the European Medicines Agency (EMEA), such as the Committee for Human Medicinal Products, the Committee for Orphan Medicinal Products, the Mutual Recognition Facilitation Group and the Pharmacovigilance Working Party. A total of 54 meetings on various areas were attended at the EMEA from 1st May up to end December 2004.

Malta became a full member of the WHO International Monitoring Programme, on 13 October 2004 and is the 75th member country. Malta has actively participated in the WHO Programme for International Drug Monitoring Annual Meeting held in Dublin in October.

Following an ongoing process for the ratification of the European Pharmacopoeia Convention that spanned several years, Malta has been accepted as the 35th member of this Convention in November. The ratification will enter into force on the 5th of January 2005, and until then Malta holds an observer status. A delegate has been nominated as member of the European Pharmacopoeia and has attended the 120th session that was held in November. An opportunity for training has already been offered by the European Directorate for the Quality of Medicines.

The Inspectorate and Enforcement Director joined the Heads of Enforcement Group of the EU member states. This group was formally set up in 2004. The remit of the group is to establish a networking activity between the Enforcement units of the Competent Authorities with the primary aim of preventing and assisting in the reduction of counterfeit drugs that find themselves on the markets of member states. Through participation in this forum the inspectorate can gain access to sensitive information and can build up on the experiences and systems of more developed countries to achieve its final goal, that of providing a good enforcement strategy for the local needs, to ensure compliance with legislation, and thus optimising protection to public health.

Quality management

The Medicines Authority has established a formal quality management system, in order to be competent to satisfy its regulatory requirements and needs and the expectations of its customers. Quality is regarded as a key responsibility of all staff and is viewed as an organization-wide commitment thereby establishing a culture of quality in all activities and processes undertaken by the Authority. The first version of the Quality Manual (July 2004) for the Medicines Authority was issued. Standard operating procedures are being compiled for the different areas with a total of 64 SOPs being finalized in 2004. The quality system is managed on a daily basis by the Operations and Regulatory Affairs Manager with the support of the documentation officer. The first internal audit was carried out in October. This was undertaken by five internal auditors who by the end of 2004 received formal training in conducting internal audits.

A pre-MRA audit of the Inspectorate Directorate was held in Malta between the 18th and 25th of October. Inspectors from Denmark and Spain audited the Directorate on behalf of the EU Commission. The audit targeted the quality system. Moreover that the auditors observed the planning, conduct and reporting of a GMP inspection by the Medicines Authority's inspectors. One of the largest local manufacturing companies was selected for the purpose of this audit. The final report has been received in mid December. In general there are some factors within the Quality System that need rectification. These include inclusion of SOP's and other amendments to fully comply with the EU system. A positive report was received on the GMP inspection and the auditors were well satisfied. The report also concluded that the relevant EU Directives had been transposed and concluded that the Canadian Audit could be recommended. This was the first audit wherein the systems of the Inspectorate Directorate were fully scrutinized by a foreign body. The audit was a useful exercise which brought much satisfaction and confidence to the staff and confirmed that a good system was in place.

One auditor attended audit training at the EMEA in preparation for the EU benchmarking audit which will take place in the first half of 2005.

Licensing

During 2004 the main activity for the licensing of medicinal products was for the issue of national market authorisation of products that were on the transition list. The approximately 7,500 products that

were on the local market in November 2002 had been included in a 'transition list' and Malta was granted a derogation period up to December 2006 to issue national market authorisations for these products. The process was to be coordinated in two steps: first a provisional market authorisation (PMA) was to be granted to be followed by a full market authorisation (MA). By the end of December 2004 applications were received for 2,289 products. All went through the first stage and PMAs were issued for 2,149 of these. The list of PMAs is published on the Medicines Authority website. Assessment of these products will be followed by the issue of market authorisations.

As from 1st May 2004 Malta started participating actively as a concerned member state in the EU Mutual Recognition Procedure (MRP), with 43 applications being received.

By the end of 2004 legislation and framework for the issue of parallel import licenses was in place. No applications were yet received. The legislation transposing the clinical trials directive (Directive 2001/20/EC) was published and the guidelines were in final draft form.

Some of the articles of Directive 2007/24/EC were transposed early, particularly article 126a of this Directive which allow the issue of a qualified licence for medicinal products where a requirement for the product is justified for public health reasons. The process and guidelines for the implementation of the procedure were in final draft stages. The Medicines Authority actively participated in the Committee which was set up by the Superintendent of Public Health to identify the list of substances/products eligible for a qualified licence.

In preparation for the implementation of the new legislation on traditional herbal medicinal products Directive 2004/24/EC which will come into force in November 2005 a guideline was set for stakeholders. Various meetings were held with individual importers and the list of traditional herbal medicinal products which were on the market before 31st March 2004 (and will benefit from 7 years transition) was compiled and was being confirmed by stakeholders. There were 460 products notified on the list, 339 (74%) of which were of European origin.

A system for the registration of homeopathic medicinal products was mapped and guidelines for stakeholders were being drafted.

Quality assessors were involved in the linguistic check process as part of the translation of the documentation for the centrally authorised products. By 1st May this process was carried out for 192 products however it was then suspended as Malta was then granted a 3 year derogation period for translation of official documentation into Maltese.

Post-licensing

The Twinning Project supported two main areas in post-licensing – the implementation of an appropriate pharmacovigilance system and dossier assessment for variations of marketing authorizations. A Policy Document for the Strategic Direction for the Set-up of a Pharmacovigilance System was drawn up. The legislation to support the pharmacovigilance system was published.

The activity in pharmacovigilance and adverse drug reactions (ADRs) reporting for 2004 consisted of 13 individual case safety reports (ICRs) from healthcare professionals in Malta, 12 CIOMS forms of ADRs occurring locally forwarded by industry, 27 non-urgent information requests, 8 rapid alerts, 23,631 CIOMS forms of ADRs originating in third countries and 173 periodic safety update reports. Analysis of the ADRs received showed that the pharmaceutical industry was responsible for most ADR reports submitted in 2004. Hospital healthcare professionals (doctors and pharmacists) and community pharmacists also submitted ADR reports to the Medicines Authority. The current data probably reflects a situation of significant under reporting, however with increased awareness amongst healthcare professionals, the reporting rate is expected to increase.

Three seminars were held in 2004, one to launch the ADR reporting system in May, followed by another two information sessions, one at St Luke's Hospital and one at Gozo General Hospital on 5 August 2004. The first issue of the drug safety bulletin was published together with an article about Pharmacovigilance and ADR reporting in the Malta Medical Journal.

A total of 5 variations to market authorizations for applications received through the mutual recognition procedure were processed.

Since accession into the European Union and the coming into force of Legal Notice 400 (2003), regulating the advertisement of medicinal products, the Medicines Authority has become responsible for the monitoring of activities relating to advertising. The activities include monitoring advertising material, handling 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 and enforcement in relation to materials not complying with the Regulations. Overall the Directorate addressed 20 formal queries on implementation of the advertising regulations and completed assessment and follow up evaluations of fourteen advertisements and promotional activities of medicinal products. The promotional activities included video productions, printed advertisements on newspapers, magazines, journals and outdoor billboards, audio advertisements and promotional seminars and meetings with stakeholders.

Inspectorate and enforcement

During the Twinning Project a number of training sessions were undertaken, both locally and abroad, by the Inspectorate staff. The areas covered included Good Manufacturing Practice (GMP), Good Distribution Practice (GDP), enforcement, and management issues. A number of shadow inspections were also undertaken in the UK. This process led to the identification and understanding of the various issues that are essential for the setting up of an Inspectorate Directorate that respects and fulfills the EU standards. It also aided in the confidence building of inspectors and to better appreciation of the responsibilities involved. The twinning experience has also led to the establishment of reference contacts and the achievement of a good working relationship with foreign colleagues**.** One of the major set-backs to the project was the fact that staff recruitment was delayed. This resulted in a situation where all the training identified and allocated for this Directorate had to be provided within the last five months of the project and the new staff had to undergo an intensive training schedule within a very short period.

During 2004 the following applications for manufacturing authorisations were processed: two applications for the renewal of licence, one application for issue of a new licence and one application for the inclusion of additional activities on a licence. In these cases the manufacturing facilities were inspected by the medicines inspectors of the Medicines Authority. In some instance GMP inspectors from the MHRA were also present to provide training and assist in the inspection process. Manufacturing licences started being issued according to the new format as established by the EU system. A new system was also initiated whereby the full inspection report was forwarded to the Qualified Person of the company to comply with EU requirements.

A request was received for the renewal of licence of an Active Pharmaceutical Ingredient (API) manufacturing site. The site was inspected and a temporary licence was issued on the condition that the facility will have to be upgraded to GMP standards by November 2005, when the new EU legislation regarding API`s will come into force. Four applications for variation of a manufacturer's licence were processed and new licenses were issued within the stipulated time frame of 30 days. These variations did not require an inspection since they targeted administrative issues. A local testing laboratory was inspected. The medicines inspectors were accompanied by a UK GMP inspector who additionally provided some training in this field.

The responsibility of issuing Certificates of Pharmaceutical Products (CPP`s), or export certificates, was taken over from the Public Health Department in June 2004. Since then 15 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.

The issue of licences for wholesale dealing in medicinal products, which was previously within the remit of the Department of Public Health, was taken over by the Medicines Authority in October. At present eighty companies are in possession of a wholesale dealer's licence. New application forms were set up together with aide memoirs to help in the inspection plan. New inspection report and licence formats were also finalised. All these documents and processes are in line with the defined EU system. The inspectors inspected wholesale dealers on a first time basis with the scope of identifying any deficiencies and giving enough time for the necessary changes to be effected gradually. Five applications for import licences were received from applicants in possession of a wholesale dealer's licence. This is a new activity that needs to be regulated following the accession into the EU. All applicants were visited by the inspectors in order to assist them in the adoption of standards during the transition phase. A final GMP inspection will be carried out before a licence is issued. Seven new applications for a wholesale dealer's licence have also been received.

143 inspections of retail pharmacies were carried out with 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. These inspections were carried out in conjunction with the Department of Public Health. Nine spot checks were carried out on pharmacies. These were initiated following reports and/or complaints from other departments, stakeholders or the general public.

Four cases of enforcement inspection and investigation were initiated and the investigations were still underway. The Medicines Inspectors provided their services as witnesses in 20 court cases for prosecution proceedings initiated against offenders.

As part of their obligation to safeguard public health Market Authorisation Holders are required to notify the Medicines Authority of any quality defect in respect of their products. An EU system of dealing with these reports was put in place. The Inspectorate adopted this system and integrated it in its quality system. A cascade system was devised to notify all health professionals of any batch recall, even after normal working hours. During the year 2004 the Inspectorate received and processed 63 reports of quality defects. 58 reports were received from foreign companies and 5 from local companies or national competent authorities. 4 batch recalls were affected following these reports. No batch recalls were initiated or reported by local manufacturing companies in respect of the products within their portfolio.

As part of the requirements of L.N. 143 and 154 of 2004 Qualified Persons need to be assessed by the National Competent Authority in order to be deemed as eligible to be named on a manufacturers licence. In this context the Inspectorate Directorate initiated two calls for applications, one in April and another in October inviting interested candidates to apply for Qualified Persons status. Applications were received for two categories, namely: permanent QP`s (these candidates must have had two years experience in a senior position in manufacturing of medicinal products) and 'grandfather' QP`s (these candidates must have had at least 6 months' experience prior to 1st May 2004 or within 12 months thereafter). Nineteen and five applications were received for the first and second sessions respectively. Interviews were conducted by a panel from the Medicines Authority. A foreign GMP expert also participated in the interviews and assisted and provided valuable advice to the Medicines Authority on the *modus operandi* to carry out such interviews.