# 2012

# Annual Report

AWTORITÀ DWAR IL-MEDIĊINI

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# Review by the Chief Executive Officer

***Dr. Patricia Vella Bonanno***

The Medicines Authority's remit is to protect and enhance public health through the regulation of medicinal products and pharmaceutical activities. The Medicines Authority achieves its remit through its core activities, by its active role with stakeholders in the sector and through its European activities. This report presents the wide range of activities carried out by the Medicines Authority during 2012.

The core activities of the Medicines Authority involve assessment and recommendations for authorisation regarding new and active authorisations of medical products and inspection and recommendations for licensing of pharmaceutical activities. Once authorised, medicinal products continue to be monitored through pharmacovigilance, the management of quality defects and the market surveillance programme. During 2012 the processes were impacted by an industrial action for a period of three months. During this period, continuity of critical operations was prioritised and resources were focused on minimising disruption to operations and stakeholders.

The Medicines Authority has an active role at Council meetings and within the European Regulatory Network. National legislation was updated through the transposition of European Directives which were aimed at strengthening of pharmacovigilance activities and the prevention of entry of falsified medicines in the supply chain. The Authority also worked on better regulation initiatives to minimise administrative burden in line with Malta's targets.

During 2012, there has been particular emphasis on review of most processes with increased adoption of a risk based approach and prioritisation for activities, increasing the effectiveness and efficiency of processes, the strengthening of information systems and of the quality management system.

# 1.0 Organisation

## 1.1 Leadership and Management

During 2012, the Medicines Authority fully achieved the main activities of its corporate management cycle. These activities included the compilation of an Operational Plan at the beginning of the year and formal review of its achievement at mid-year, the Medicines Authority Business Plan, Management Review at mid-year and performance appraisals for employees which are performed twice a year. Seven (7) Management and three (3) Interface meetings were held.

## 1.2 Customer Satisfaction and Communication with Stakeholders

In 2012, the Medicines Authority engaged into a number of proactive initiatives to enhance communication with stakeholders in line with feedback received during a stakeholder survey carried out in 2011. The initiatives included:

- Participation and poster on the benefit risk assessment of medicines and new pharmaceutical legislation for the Malta Medical School Conference targeting medical practitioners.
- An article targeted to healthcare professionals on enhancing the choice and use of medicines
- An article on L-Għażla Magazine which is distributed to all households in Malta and Gozo on the safety of medicinal products targeting
- Participation on four TV and radio interviews targeted to the general public
- Publication of an information leaflet in collaboration with Malta Enterprise targeting prospective industry.

The Authority regularly communicated with stakeholders through circulars and these were uploaded on the website so as to ensure transparency. The website was updated with relevant information and continuous update of the list of Authorised Medicinal products (together with the summary of product characteristics and the package leaflets) and the list of licensed pharmaceutical activities.

During 2012, three (3) complaints files regarding pharmaceutical activities were opened. This excludes complaints related to enforcement and advertising of Medicinal Products for which there is a separate

procedure. Two complaints were closed by end of the year and one was ongoing as on 31st December 2013.

## 1.3 Quality Management

A Quality Manager was recruited and started working with the Medicines Authority as from April 2012. During 2012 there was a full review of the Quality Manual also taking into consideration feedback from staff on Mission, Vision and Objectives.

Forty five (45) standard operating procedures, most of which were at the stage of the second or third issue, were reviewed. The review addressed gaps arising from the new Pharmacovigilance legislation and also gaps and targets of the Benchmarking of European Medicines Agencies (BEMA). Moreover the review incorporated changes in policies as well as corrective and preventive action identified through implementation of operations, internal audits and Management Review. Staff members were given training on reviewed standard operating procedures.

A three-year audit strategy was drawn up and this was complemented by an annual audit programme for 2012 – 2013. A number of internal auditors were trained / re-trained so as to have a team of internal auditors. During the internal audits performed during 2012, a number of corrective and preventive actions were identified which should be addressed with the aim to improve the quality of operations within the Medicines Authority. Their implementation is monitored by the Quality Manager.

An annual Management Review was performed in August 2012, during which the Quality Management System as detailed in the Quality Manual was reviewed. Also, this involved review of the operations of each Unit and Directorate within the Medicines Authority, evaluation of results of stakeholder (internal and external) feedback, including complaints; evaluation of results of previous audits (internal and external); and analysis of quality improvements. This resulted in a number of action points. This aims to ensure continuous improvement and the continued suitability, adequacy, and effectiveness of the Quality Management system.

During 2012, one hundred and nineteen (119) quality improvements were registered in the Quality Management Systems. These include reviews of Standard Operating Procedures and amendments to standard documentation. This increase is attributed to a number of standard operating procedures which

were due for review and also a number of quality improvements identified during audits. In fact, circa 44% of quality improvements identified resulted from internal / external audits.

The Medicines Authority is participating in the third Benchmarking of European Medicines Agencies (BEMA III). In preparation for the BEMA visit, which is scheduled for April 2013, a number of self-assessment reports were completed against targets for BEMA III.

## 1.4 Human Resources Management

During 2012 there was review of the Collective Agreement and the Collective Agreement was signed on the 6th of December. There were three months industrial action and during this period the Medicines Authority adopted business continuity measures to ensure that critical operations were covered as well as possible.

The number of persons employed by the Authority at the end of 2012 was 36 (2011: 42).

| | 2012 Female | 2012 Male |
|---|---|---|
| Management | 3 | 4 |
| Technical staff | 15 | 8 |
| Administration | 5 | 1 |
| | 23 | 13 |

**Table 1 - Number of persons employed by the Authority at the end of 2012**

Training and development priorities for 2012 were set and staff had the opportunity to attend training and development initiatives both in Malta and in European Countries in line with needs and resources of the organisation. Areas for training for 2012 included training on environmental risk assessment, the trends within Good Manufacturing Practice inspections, Microsoft access, management of teleworkers, ISO 9001 and internal auditing.

During 2012, the Medicines Authority formalised an Equality Policy and applied for the Equality Mark. Information on equality and gender mainstreaming was distributed to all staff.

Four staff meetings were held during 2012. During the staff meetings, important decisions were communicated, initiatives were taken to motivate staff and employees had the opportunity to discuss and share their opinion on the way forward of the Medicines Authority.

## 1.5 Information Systems Management

During 2012 the Information Systems Department continued to operate and maintain the core and European information systems and ICT infrastructure. The business processes of all activities carried out at the Authority were mapped out using the Universal Modelling Language and the business requirements for a new Licensing Management System were defined. The tender document of the new information system was written with the support of the Malta Information Technology Agency and submitted to the Department of Contracts in October. Software development on a new website for the Medicines Authority was finalised and staff members were trained in the usage of the content management system and the content uploaded.

During the first six months of the year, the National Audit Office (NAO) carried out an audit of the Information Systems Department. Recommendations were taken up and implemented. An internal audit was carried out to verify that the NAO recommendations were implemented.

The Malta Drug Information System was migrated to a more robust hardware platform. The new platform includes replication of the database to the backup data centre at Mater Dei Hospital. The EURS is Yours review tool was implemented and users trained by a foreign expert from the vendor (Extedo). A contract was signed with MITA for the provision of the hosting environment. A multi-functional machine was

procured and this replaced legacy hardware. The initiative was also intended to encourage employees to scan documents rather than photocopy or print.

The Medicines Authority laptops were upgraded to Windows 7 and full-disk encryption and the Trusted Platform Module were enabled. This ensures that sensitive data stored on laptops is secure. Moreover, overseas insurance was purchased for the laptops. Dual screens were installed for senior pharmacists to enhance their experience when reviewing pharmaceutical dossiers. This project will also help reduce printing.

The Authority is participating in the Common EU Submission Project (CESP) and was a member of the first group of national competent agencies to receive submissions from applicants via the portal. In June the Medicines Authority hosted the Scientific Advise Working Party. The IS department provided wireless and teleconferencing services to all participants and operational support.

## 1.6 Collaboration with other Entities

During 2012, the Medicines Authority continued to collaborate with other entities, mainly the Superintendence for Public Health, the European Medicines Agency, the European Commission and other competent authorities and departments in Malta and the European Union. The Medicines Authority collaborated with the Italian Medicines Agency for assessment of medicinal products where Malta was a Rapporteur/ Reference Member State. In June 2012, the Medicines Authority collaborated with the European Medicines Agency to host the latter's Scientific Advice Working Party for a four day plenary session held in Malta. Usually the Scientific Advice Working Party meets in London at the European Medicines Agency, but due to the 2012 London Olympics, alternative venues were required, and following a successful bid, the Medicines Authority was chosen.

# 2.0 Regulatory Affairs

## 2.1 Participation in drafting new legislation

The Medicines Authority continued to participate on behalf of the Ministry on discussions on legislative proposals by the Commission, by attending meetings held under the Council and drawing up reports and instruction notes for these meetings. The main dossiers discussed in 2012 were the revision of the Clinical Trials Directive and further improvements of the 2010 legislation on Pharmacovigilance which led to the publication of Directive 2012/26/EU and Regulation (EU) No 2012/1027/EU.

## 2.2 Update and Implementation of legislation

In 2012, the Medicines Authority supported the Licensing Authority in the transposition process of Directive 2010/84/EU on Pharmacovigilance and Directive 2011/84/EU on Falsified Medicines. The following legal notices were published.

- 228 of 2012 – Medicines Authority (Fees) (Amendment) Regulations, 2012
  *Government Gazette of Malta No. 18,942 - 13.07.2012*

- 369 of 2012 – Pharmacovigilance Regulations, 2012
  Government Gazette of Malta No. 18,983 - 30.10.2012

- 370 of 2012 – Herbal Medicinal Products (Amendment) Regulations, 2012
  *Government Gazette of Malta No. 18,983 - 30.10.2012*

- 372 of 2012 – Medicinal Products (Labelling and Packaging) (Amendment) Regulations, 2012
  *Government Gazette of Malta No. 18,983 - 30.10.2012*

- 373 of 2012 – Medicines (Marketing Authorisation) (Amendment) Regulations, 2012
  *Government Gazette of Malta No. 18,983 - 30.10.2012*

- 374 of 2012 – Pharmacovigilance Inspections Regulations, 2012
  *Government Gazette of Malta No. 18,983 - 30.10.2012*

- 443 of 2012 – Control of Advertising of Medicinals (Revocation)Regulations, 2012
  *Government Gazette of Malta No. 19,003 - 14.12.2012*

- 444 of 2012 – Medicines Authority (Fees) (Amendment) (No. 2) Regulations, 2012
  *Government Gazette of Malta No. 19,003 - 14.12.2012*

- 445 of 2012 – Oral Retinoid Medicinal Preparations (Revocation) Regulations, 2012
  *Government Gazette of Malta No. 19,003 - 14.12.2012*

- 476 of 2012 - Manufacture and Importation of Medicinal Products for Human Use (Amendment) Regulations, 2012
  *Government Gazette of Malta No. 19,008 – 24.12.2012*

- 477 of 2012 - Good Manufacturing Practice in Respect of Medicinal Products, Active Substances and Investigational Medicinal Products for Human Use Regulations, 2012
  *Government Gazette of Malta No. 19,008 – 24.12.2012*

- 478 of 2012 – Wholesale Distribution and Brokering of Medicinal Products and Active Substances Regulations, 2012
  *Government Gazette of Malta No. 19,008 – 24.12.2012*

## 2.3 Better Regulation

The Medicines Authority is actively participating in the government better regulation strategy which aims at improving the quality of legislation, by enhancing the performance, cost-effectiveness, and legal quality of regulations and the administrative procedures, tariffs and fees derived thereof. As part of the Better Regulation Project, the two outdated Legal Notices on Control of Advertising of Medicinals (S.L. 443 of 2012) and Oral Retinoid Medicinal Preparations (S.L. 445 2012) were removed. Also there is a proposal for changing the registration of prescriptions within pharmacies. This was discussed with stakeholders and is being considered.

# 3.0 Assessment and Authorisation of Medicinal Products

During 2012, the Medicines Authority continued with activities towards national and European procedures whilst consolidating its operations as Reference Member State in the Decentralised Procedure. The number of authorised medicinal products in Malta (excluding products authorised through the centralised procedure) as on 31st December 2012 was four thousand two hundred and seventy three (see Figure 1 for route of authorisation).

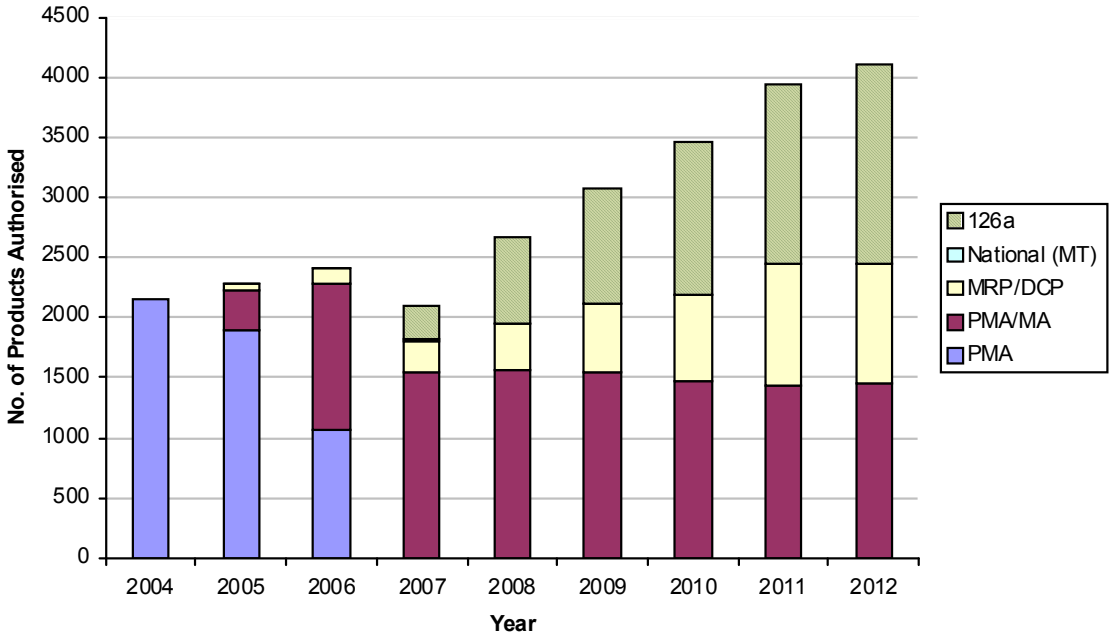


**Figure 1 – Cumulative Number of Authorised Medicinal Products in Malta (excluding products authorised through the centralised procedure) as on 31st December 2012**

## 3.1 The Medicines Review Committee

The Medicines Review Committee within the Medicines Authority continued to meet regularly to discuss regulatory and technical issues relating to ongoing applications for marketing authorisations for medicinal products, both national and European. These include applications for marketing authorisation

and post-authorisation activities (e.g. variations, renewals, pharmacovigilance issues) as well as clinical trial applications and European work-sharing procedures. Other items presented include feedback from external technical and regulatory meetings attended by members of the Medicines Review Committee and other staff members, where relevant and discussion on any guidelines that have an impact on the procedures discussed in the Committee. Meetings were held on a monthly basis.

## 3.2 European Procedures

### *3.2.1 Marketing Authorisation Procedures*

**Malta as rapporteur in the Centralised Procedure**

During 2012, Malta was rapporteur for four (4) new centralised procedures and also for variations for previous products for which Malta was rapporteur through the centralised procedure. During 2012, Malta was also the rapporteur for a re-examination procedure.

**Malta as Reference Member State (RMS) in the Decentralised Procedure (DCP)**

The total number of new procedures with Malta as Reference Member State (RMS) started was ten (10). Some of the procedures started in 2012 are currently still ongoing. Applications for abridged applications were assessed for oral dosage forms and sterile ophthalmic pharmaceutical forms. Internal training is ongoing on other pharmaceutical forms to be taken up in the future in procedures with Malta as RMS or as rapporteur, to widen the scope for participation in European procedures. The number of variations for products where Malta is RMS received was seventy five (75). Figure 2 shows the number of finalised MRP/ DCP Procedures within the EU in 2012, including Malta (MT).

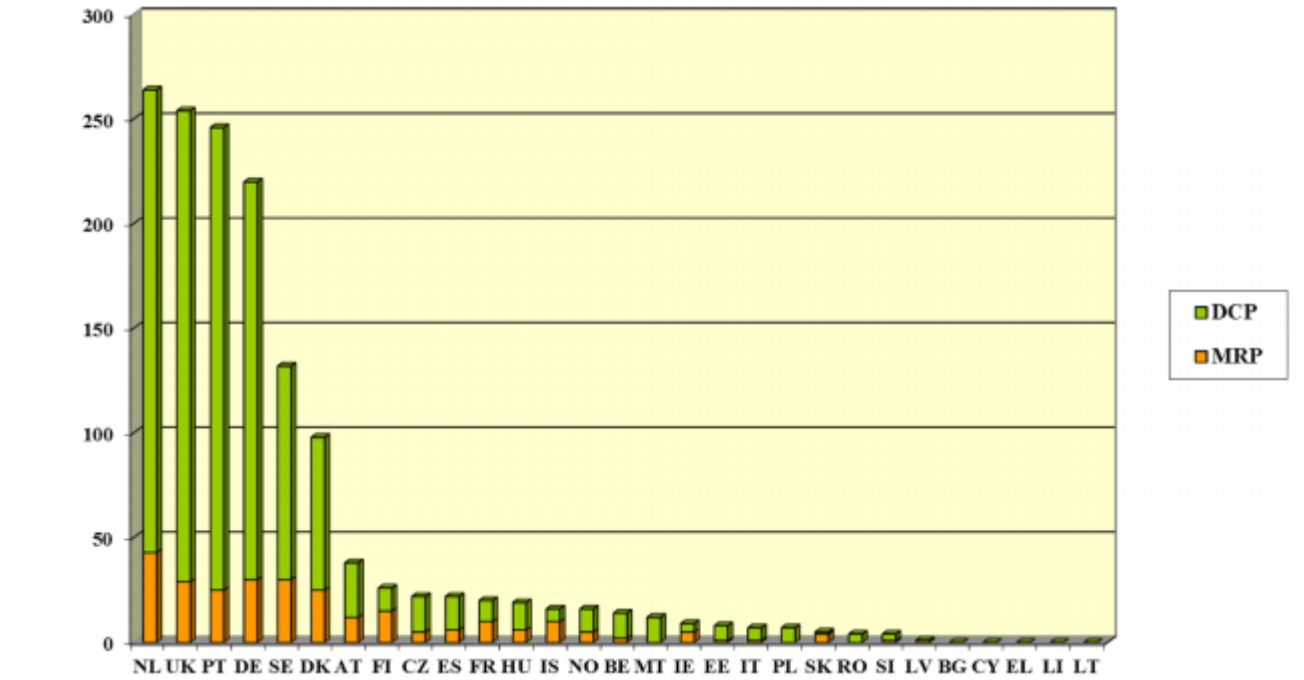


**Figure 2 –Finalised MRP/ DCP Procedures within the EU in 2012**

For procedures for which Malta is Reference Member State, team meetings are organised regularly to discuss the progress of the procedures and for a consolidated and fact-based decision to be taken at each step of the procedure. Each procedure is also discussed in the Medicines Review Committee, in particular where technical or regulatory decisions have to be taken or endorsed for a final Malta position.
Were the fees for RMS decreased in 2012? If so please include this information.

Cancellations of booked slots for RMS procedures in 2012 have continued to have a considerable negative impact. The Medicines Authority continues to strive to continue to participate actively in European procedures as a Reference Member State/ Rapporteur.

**Malta as Concerned Member State**

Two hundred and six (206) European marketing authorisation product applications were received in 2012 with Malta as Concerned Member State. Fifty four (54) were received through the Mutual Recognition Procedure and one hundred and fifty two (152) through the Decentralised Procedures. The number of marketing authorisations granted for the two types of procedures for the same period was sixty nine (69)

and two hundred and fourteen (214) respectively (Figure 3). Compared to 2011, the number of Decentralised and Mutual Recognition procedures with Malta as Concerned Member State decreased by 27%.

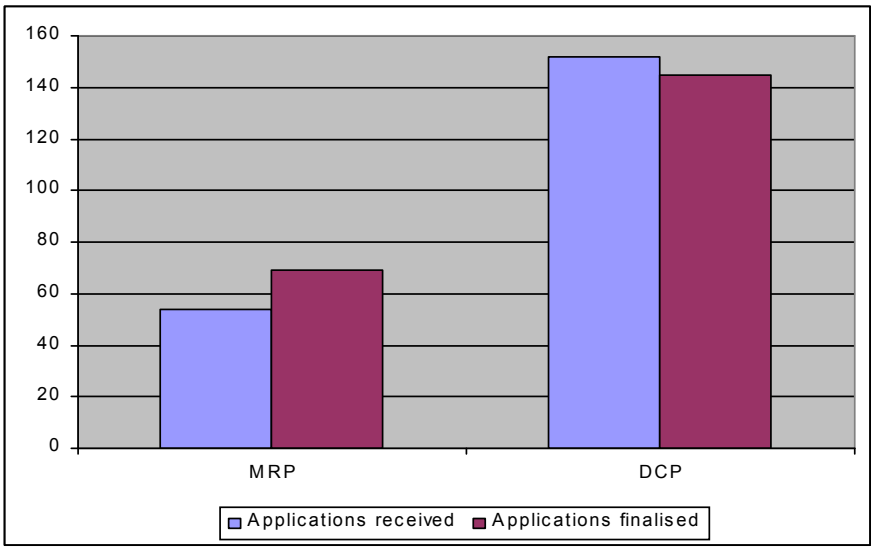


**Figure 3: Applications received and finalised for MR and DC procedures with Malta as Concerned Member State in 2012**

**European post-authorisation procedures**

One thousand two hundred and four (1204) Mutual Recognition Procedure variation applications were received in 2012 and four hundred and three (403) were finalised. These include ongoing procedures from 2011. One hundred and sixty five (165) renewal applications were received and thirty six (36) were finalised. Thirty one (31) article 61(3) notifications were received and fifteen (15) were finalised during 2012 (Figure 4).

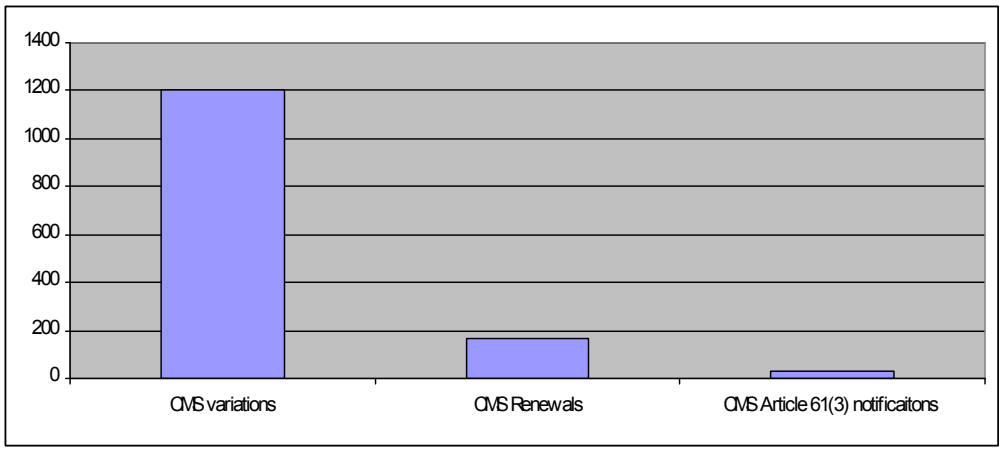


**Figure 4 - Summary of post-authorisation procedures received through the European Procedures (MRP) in 2012 – MT CMS**

### *3.2.2 Work-sharing Procedures*

Throughout 2012, the Medicines Authority participated in EU procedures at the level of the European Medicines Agency, in particular in paediatric work sharing. Malta was a rapporteur for two (2) paediatric data assessments in the European work-sharing procedure in accordance with article 45 of the Paediatric Regulation 1901/2006/EC. This procedure consists of the assessment of all data in relation to the effective and safe use of a medicinal active substance in children. The Summary of Product Characteristics and package leaflet are then updated to reflect the conclusions of this assessment. Both procedures were finalised as at end 2012. The Medicines Authority representatives at the Paediatric Committee at the European Medicines Agency in London were involved as rapporteurs or peer reviewers for twelve (12) different procedures which was similar to the data of 2011. As at end 2012, seven (7) of these procedures were concluded and five (5) were ongoing.

## 3.3 National Procedures

**National marketing authorisation applications**

A total of twelve (12) national marketing authorisation applications were received in 2012, mainly line extensions to nationally authorised products. Seventeen procedures (17) were finalised in the same period.

**Parallel import applications**

Seventy eight (78) parallel import licence applications were received and seventy two (72) finalised by the end of 2012. There has been a continued marked increase of parallel import applications during the last years as compared to previous years.

**Authorisations in accordance with article 126a of Directive 2001/83/EC, as amended**

The number of applications for authorisations in accordance with article 126a of the directive 2001/83/EC as amended received during 2012 was two hundred and eighty nine (289) and two hundred eighty five (285) authorisations were issued in the same period. A summary of the national authorisation procedures received and finalised in 2012 is given in Figure 5.

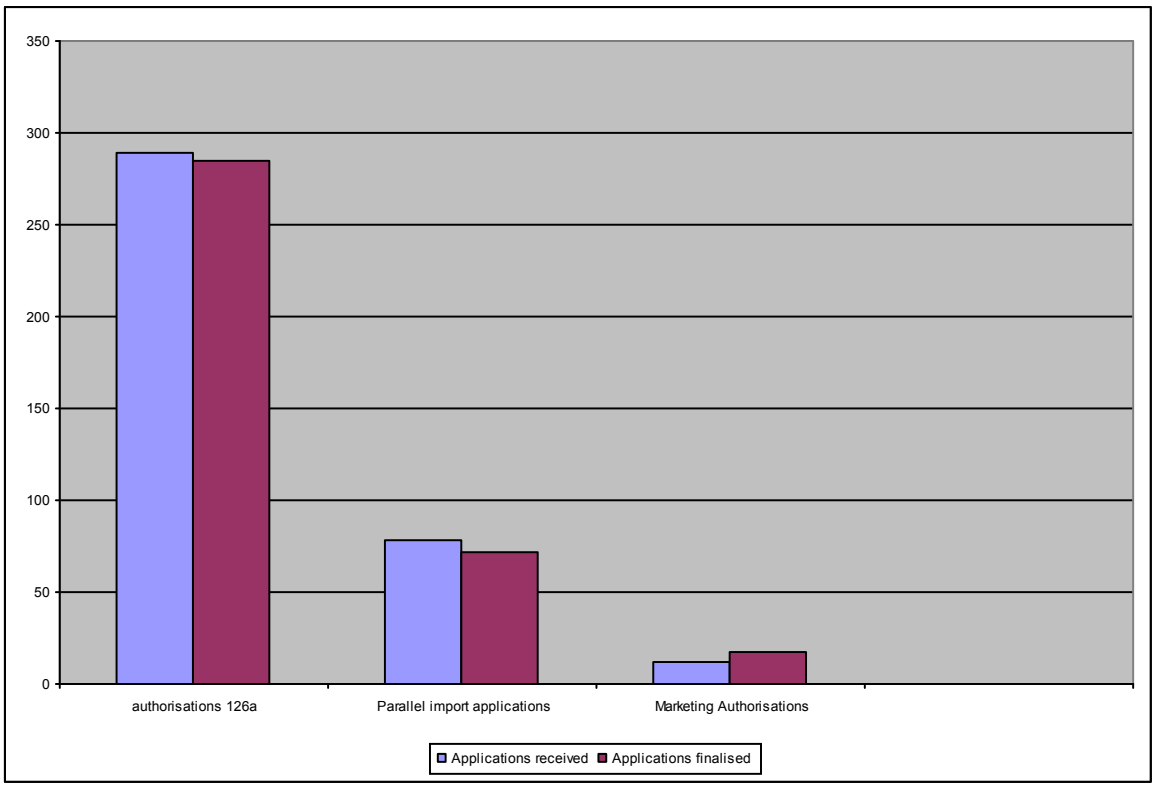


**Figure 5 - Summary of national procedures received and finalised in 2012. Some procedures were continued from previous years.**

**National variation applications**

Nine hundred ninety eight (998) national variation applications were received in 2012. Nine hundred and sixty four (964) procedures were finalised. National variations received with payment (not with an approval from another Member State) were being prioritised for assessment during 2012 .

**National notification 61(3) applications**

One hundred thirty two (132) national article 61(3) notifications were received. One hundred and fifty eight (158) procedures were finalised. These had an impact on the package leaflets of one hundred and eight products.

**National renewals**

Twenty seven (27) national renewal applications were received and one hundred and thirteen (113) were finalised in 2012.

**Transfer of marketing authorisations**

Twenty nine (29) applications for the transfer of a marketing authorisation holder were received and fifty six (56) processed.

**Withdrawals of marketing authorisations and licences**

Withdrawal of National marketing authorisations were two hundred and sixteen (216), one hundred and three (103) withdrawals for authorisations in accordance with article 126a and thirty seven (37) parallel import licences.

**Summary**

A summary of the procedures received and finalised in 2012 is given in Figure 6.

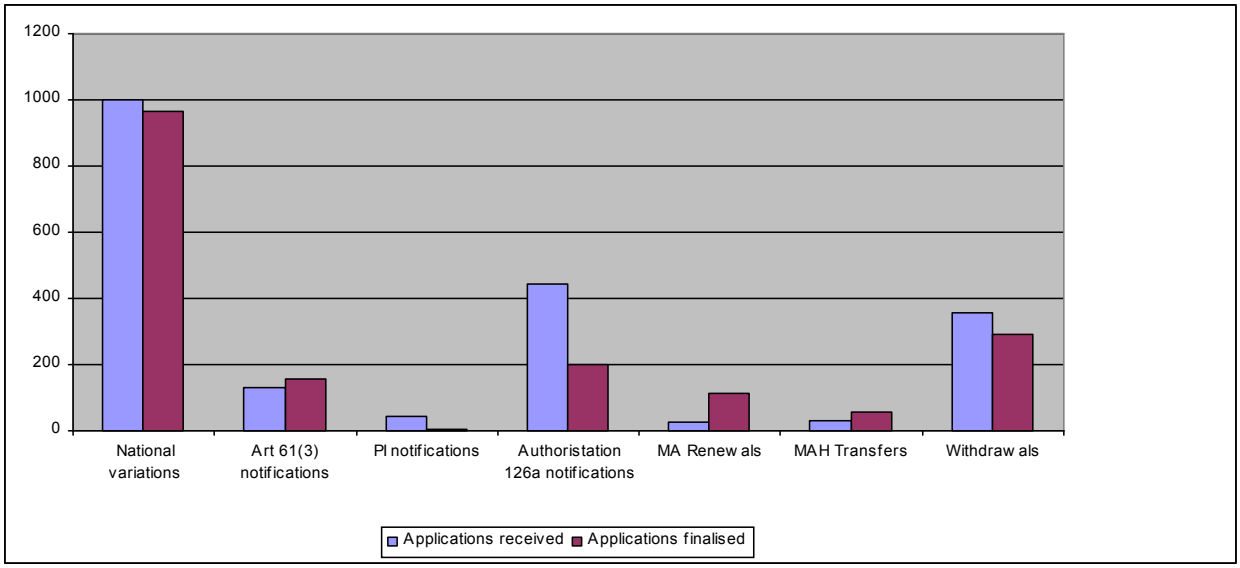


**Figure 6 – Summary of national post-authorisation procedures received and finalised in 2012**

## 3.4 Linguistic Checks of product information of products authorised through the Centralised Procedure

In 2012, the Medicines Authority continued to coordinate procedures for linguistic review of product information in Maltese. This activity is carried out for products authorised through the centralised procedure. This information is published on the EMA and Commission websites.

## 3.5 Scientific Advice

Since 2009, the Medicines Authority has set a process for scientific advice and protocol assistance requests. The applications accepted are for generic medicinal products in line with the Medicines Authority's Reference Member State activity. In 2012, no scientific advice requests were submitted to the Medicines Authority.

# 4.0 Clinical Trials

During 2012, no new Clinical Trials applications were submitted to the Medicines Authority. Six (6) amendments to trials which are being conducted in Malta were received. Eleven (11) amendments were approved in 2012. All information has been inputted in the European Database for Clinical Trials. Since 2010, there has been a decrease in Clinical Trial applications submitted to the Medicines Authority. This trend was recorded in 2011 and then again in 2012.

# 5.0 Pharmacovigilance

The main objectives of the Pharmacovigilance role of the Medicines Authority includes the evaluation, monitoring and, where appropriate, implementation of regulatory action to maximise benefit and minimise risks associated with medicinal products. The Medicines Authority has in the past year, maintained an active role in Pharmacovigilance.

## 5.1 National Pharmacovigilance Activities

The Medicines Authority endeavours in a number of activities to ensure that only safe medicinal products are kept on the Maltese market. The collection, investigation and reporting of drug safety information (the Spontaneous Reporting System) in accordance with European requirements comprises one such major Pharmacovigilance activity carried out by the Medicines Authority. The Medicines Authority requests the implementation of risk minimisation measures that are part of conditions of marketing authorisations from marketing authorisation holders as well the approval of Direct Healthcare Professional Communications required to send key messages to prescribers and suppliers of medicines. The Medicines Authority also requests modifications to be implemented to medicinal product information following safety signal detection activities by the European Medicines Agency and the opinions adopted by its Committees. Safety information updates as supplied by the medicinal products' Marketing Authorisation Holders are also assessed and followed up at a local level. These may sometimes also result in the implementation of product safety recalls in an effort to ensure public safety. The Medicines Authority assesses and monitors risk management programmes as proposed by Marketing Authorisation Holders or as recommended on a European level. The Authority also participates in discussions related to safety of medicinal products at European level.

The Medicines Authority utilises a number of European information technology application systems and networks for the implementation of the above-mentioned activities. The collection of safety information from local healthcare professionals comprises the major and most basic Pharmacovigilance activity and this is furthered by the collation of these reports using these European IT applications such as EudraVigiliance (EV) and EV Data Analysis System (EV DAS). Reports detailing occurrence of adverse drug reactions to medicinal products available on the market or at hospital are regularly submitted to the Medicines Authority for review and assessment. Such adverse drug reaction reports are mainly compiled

and reported by healthcare professionals or the local Marketing Authorisation Holder representatives for the medicinal product.

Wherever medicines are being used, there should be a readiness to observe and report unwanted and unexpected medical events. The Medicines Authority strives to foster an attitude of participation by promoting the need for drug safety monitoring in all its collaborations with marketing authorisation holders as well as healthcare professionals.

A total of one hundred and fifty three (153) Individual Case Summary Reports (ICSRs) were registered over 2012. Each of these cases detailed at least one adverse drug reaction to the medicinal product concerned thus resulting in a total of three hundred (300) individual adverse drug reactions. Figure 7 gives a breakdown of these adverse drug reactions according to system organ classification. Each case report was assessed by the Medicines Authority and reported electronically to the European Medicines Agency and the World Health Organisation as the central adverse drug reaction repositories. Adverse drug reaction databases maintained at these organisations typically comprise essential medicinal product safety monitoring tools which allow for the identification of potential/novel safety signals associated with the use of specific drugs particularly when these are administered at certain doses and/or to distinct patient categories.

Figures 8 and 9 further classify the adverse drug reaction case reports (as received over 2012) according to seriousness and patient age respectively. The severity of the adverse drug reaction reports is normally assigned by the reporting healthcare professional or by the Medicines Authority following careful assessment and consideration of applicable factors such as dose of the medicinal product, indication for use, concurrently administered drugs and underlying patient disease.

The establishment and maintenance of a viable electronic reporting system with the European Medicines Agency and the World Health Organisation has comprised a major Pharmacovigilance endeavour necessary for the reporting of adverse drug reactions according to European legislative requirements. Over 2012, the use of the European electronic reporting systems (specifically the use of the EudraVigilance network) was sustained and further validated by the Medicines Authority for purposes of determining proper case reporting by the Marketing Authorisation Holders at a local level and subsequent case collation within a centralised European database. This task helped ensure population of the European database with all adverse drug reaction reports originating in Malta, and thereby allowed for European-

wide safety risk assessments to be performed whenever necessary and on any of the currently authorised medicinal products.

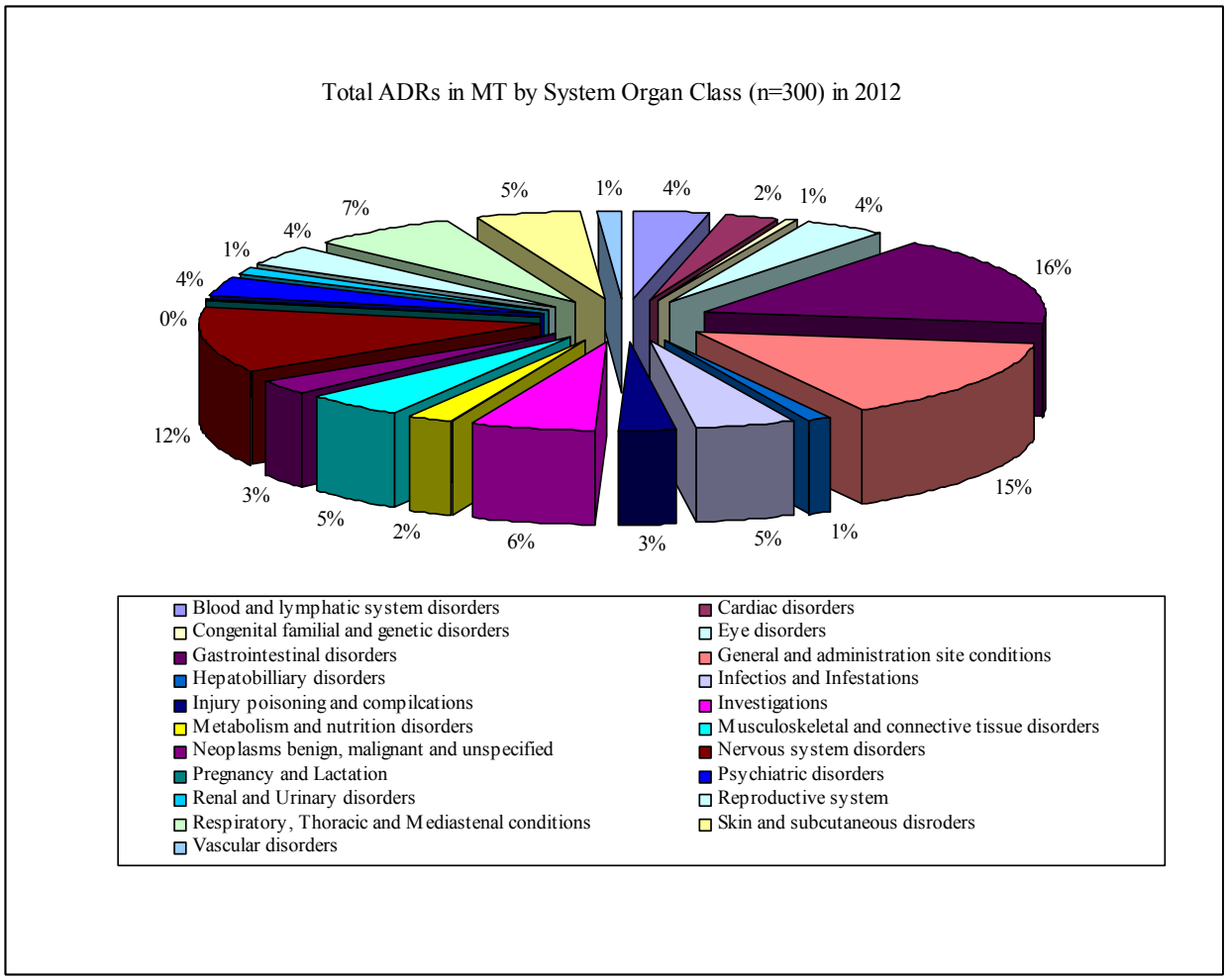


**Figure 7: Distribution of Adverse Drug Reactions according to System Organ Classification in 2012**

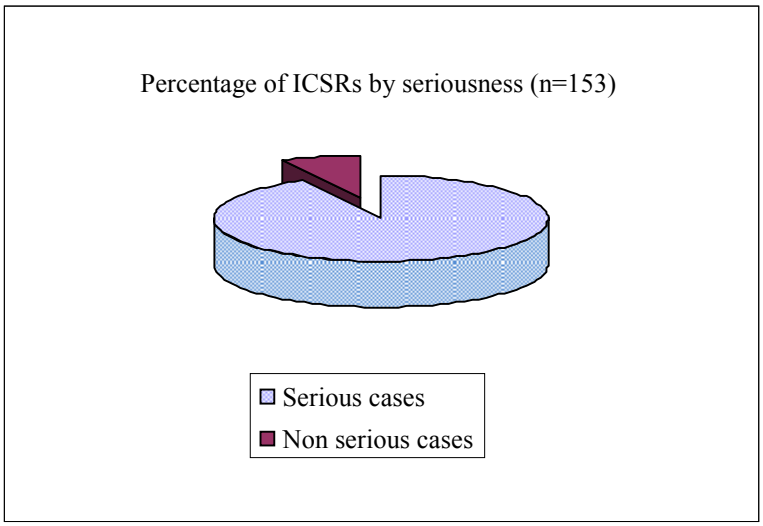


**Figure 8: Frequency of ICSRs according to seriousness in 2012 (n=153)**

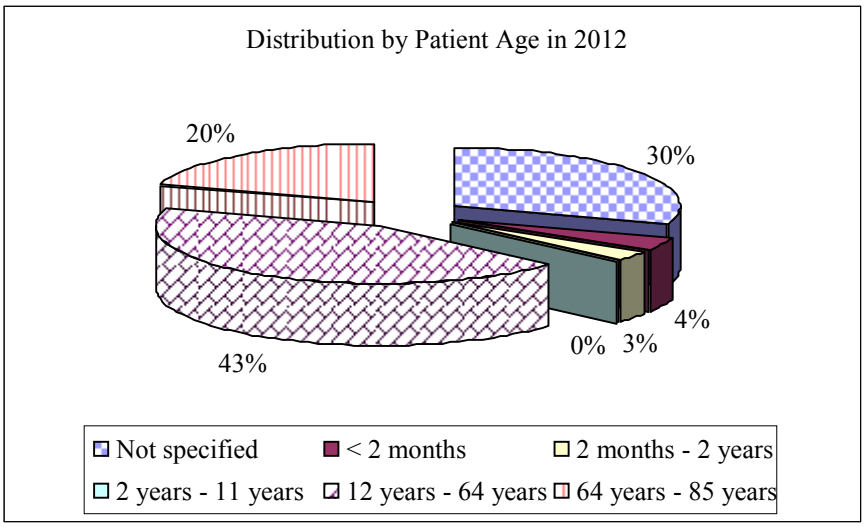


**Figure 9: Percentage distribution of case safety reports according to patient age 2012**

The Medicines Authority is also responsible for ensuring medicinal product safety via the assessment and approval of circulars detailing proposals for safety updates to scientific product information. Approval of such information is normally requested by the concerned product's Marketing Authorisation Holders or its local representative. The Medicines Authority may, on the other hand, initiate such requests for product safety updates following toxicological signal identification and expert working party or committee decisions taken at European Medicines Agency or World Health Organisation level. Requests may also entail product suspension or recall.

Other activities are undertaken by the Medicines Authority for purposes of attaining effective product safety surveillance, amongst which are the (1) Communication as relevant with the Department of Healthcare Services Standards on toxicological risks identified in relation to blood products (Haemovigilance); (2) Initiation and subsequent approval of variations to scientific medicinal product information relating to identified novel or increased risk (Urgent Safety Restrictions); (3) Investigation into locally reported incidences of severe unexpected medicinal product toxicity or any anomalous lack of efficacy following medicinal product administration (Local Product Safety Issues). (4) Review of newly emergent data concerning safety evidence of a medicinal product, substance or class upon request. (5) Review of queries that may be related to a possible safety issues with a medicinal product, substance or class. Table 2 below gives the distribution of reviews, communications and approvals which the Medicines Authority post-licensing directorate handled over 2012.

Coupled with this, any queries related to Pharmacovigilance activities are attended to by the post-licensing directorate. The main area of queries were those relating to the collection, assessment and reporting of local adverse drug reactions by healthcare professionals and Marketing Authorisation Holder representatives (Table 3). The latter communications are denoted by the abbreviations: ADRs/SUSARs/PSURs/EudraVigilance.

| Documents Received | Number of submissions |
|---|---|
| PSURs | 1418 |
| Risk Management Plans | 169 |
| Line Listing/SUSAR/DSURs | 10 |
| Annual Reassesments | 11 |
| Direct Healthcare Professional Communications | 38 |
| Safety Circulars | 15 |
| Other Circulars | 1 |
| Risk minimisation measures | 19 |
| Rapid Alert | 4 |
| Non Urgent Information | 11 |
| | |

**Table 2: Pharmacovigilance and safety issue reviews and communications – 2012**

| | Query | |
|---|---|---|
| **ADRs** | Testing requirements | 15 |
| | Request for acknowledgments | 6 |
| | Literature report requirements | 1 |
| | Queries on guidance document on Eudravigilance P/002 | 13 |
| | Causality assessments/ evaluation | 5 |
| | TOTAL | 40 |
| **PSURs** | Format; NeeS or eCTD/Eudralink/email or cd | 3 |
| | Renewals and PSURs | 2 |
| | Requirements for 126a products and centralised | 3 |
| | Request for acknowledgment of PSUR receipt | 5 |
| | TOTAL | 13 |
| **Clinical Trials** | SUSARs/DSURs/LineListings | 6 |
| | TOTAL | 6 |
| **Pharmacovigilance legislation** | National requirements for ADR submission, status of national legislation, request for guidelines | 16 |
| | EU-QPPV or Drug safety responsible requirements | 4 |
| | TOTAL | 20 |
| **Other** | Requirements for submission of Risk Minimisation Measure | 5 |
| | Requirements for submission of DHPCs | 4 |
| | Advertising | 4 |
| | PSMF | 1 |
| | Request for information by consumers | 1 |
| | Named patient basis programmes | 1 |
| | **TOTALS** | **95** |

**Table 3: Pharmacovigilance related queries in 2012 (n=105)**

## 5.2 New Pharmacovigilance Procedures by the Medicines Authority

Malta finalised initiated its second PSUR-assessment under the European work-sharing procedure in 2012. The first one Pharmacovigilance inspection was performed as collaboration with inspectorate Directorate. These inspections are done on marketing authorisation holders who have their Pharmacovigilance headquarters in Malta. In 2012, Directive 2010/84/EU on Pharmacovigilance was transposed and the preparation for the new changes in legislation carried over 2011 were implemented in 2012. Work on the redesign of the national ADR report form in order to improve the collection of data on ADRs and to enable the capture of medication errors was finalised in 2012.

During 2012, a number of discussions were held among various directorates within the Medicines Authority with the specific purpose of upgrading and streamlining quality systems in respect of currently applied Pharmacovigilance methods and processes. Work instructions were drawn up in line with adopted practices particularly in respect of safety circular compilation, the assessment and approval of additional risk minimisation measures as well as the assessment and approval of Direct Healthcare Professional Communications (DHPCs).

# 6.0 Inspection and Licensing of Pharmaceutical Activities

The Medicines Authority is responsible for inspecting and recommending the issue of licences for manufacturers and wholesale dealers according to national legislation and EU Good Manufacturing Practice (GMP) and EU Good Distribution Practice (GDP) respectively, whilst pharmacies are inspected against national legislation and standards. The Medicines Authority also carried out Good Clinical Practice inspections of clinical trials on a risk based approach and also started for the first time in 2011 to carry out Pharmacovigilance inspections which it continued in 2012. Table 4 shows the number of authorised pharmaceutical activities in Malta.

| | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|---|---|---|---|
| GMP authorised sites | 5 | 6 | 11 | 18 | 21 | 24 | 28 | 32 | 33 |
| Wholesale Dealers | 82 | 74 | 66 | 69 | 74 | 72 | 71 | 71 | 70 |
| Community Pharmacies | 208 | 206 | 207 | 207 | 208 | 209 | 211 | 215 | 219 |

**Table 4: Authorised Pharmaceutical Activities in Malta (Cumulative) as on 31st December 2012**

In 2011, the Medicines Authority started to assign a risk rating according to a Quality Risk Management (QRM) tool developed at PICS and adopted by the Medicines Authority which it continued throughout 2012. Thus, by the end of 2012, the Medicines Authority established its task of assigning a risk rating to all GMP & GDP operators. This would help in work prioritisation and in the devising of inspections plans based on a risk based approach also for GMP & GDP inspections. All currently licensed activities are regularly inspected on a two year cycle. These include all pharmacies, all wholesale dealers, all importers, all full line manufacturers and re-packagers. The only exception to this is those which are issued with only a GMP certificate (valid for three years) but not with a license. Now with all entities having a risk rating inspection frequency can vary from once every year or less for those considered as being of a higher risk, once every three years for those considered having a low risk and once every two years for the others which are considered as having a medium risk.

Two Good Clinical Practice (GCP) inspections were identified based on a risk based approach, carried out and successfully concluded in 2012. For the second year, the Medicines Authority also continued with its Pharmacovigilance inspections in its annual inspection plan.

## 6.1 Participation of Inspectors in international fora

During 2012, the Medicines Authority continued its involvement in the international GMP fora through its participation in Pharmaceutical Inspection Co-operation Scheme (PIC/S) meetings and seminars. The Authority continued to participate proactively through its members of staff in the PIC/S meetings, seminars and expert working circle particularly on QRM where the QRM tool was finalised at PICS level and adopted by the Medicines Authority.

The Inspectorate and Enforcement Director of the Medicines Authority is the group leader for work-stream within the Heads of Medicines Agencies Working group for Enforcement Officers whereby differences between member states in WDL/Enforcement legislation and inspection/enforcement procedures are studied. Inspectors participate regularly in the following meetings held at the European Medicines Agency; the Good Manufacturing and Distribution Practice (GMDP) Inspectors Working Party (held four times a year); the Good Clinical Practice (GCP) Inspectors Working Party (held four times a year) and the Pharmacovigilance (PhV) Inspectors Working Party (held also four times a year). Apart from these, the Inspectorate and Enforcement Director attended regularly Commission and Council and Committee meetings on the issue of Directive 2011/62/EU and delegated and implementing acts issued under same directive.

## 6.2 Manufacturing and Importation Authorisations (MIAs)

During 2012 the Medicines Authority carried out thirteen (13) GMP inspections for new or renewal of GMP licences/certificates as follows, out of which there were one new application for partial manufacturing; one new application for an importer's licence from a non-MRA country and one new application for an Active Pharmaceutical Ingredient (API) manufacturer [total of three (3) new GMP applications and inspections].

Six (6) Manufacturing Authorisations (MAs) inspections were carried out; one (1) for an active pharmaceutical ingredient and two (2) for non sterile solid dose manufacturers; five (5) inspections for MAs for repackaging and re-labelling / partial manufacturing operations; five (5) inspections for MAs of

importation activity: three from countries which have Mutual Recognition Agreements (MRAs) with the EU for GMP and two from countries which do not have an MRA.

A total of thirty two (32) MAs variation applications were processed in 2012 for manufacturers and importers, out of which two (2) required an inspection. Cumulative number of EU GMP authorised activities is shown is Figure 10.

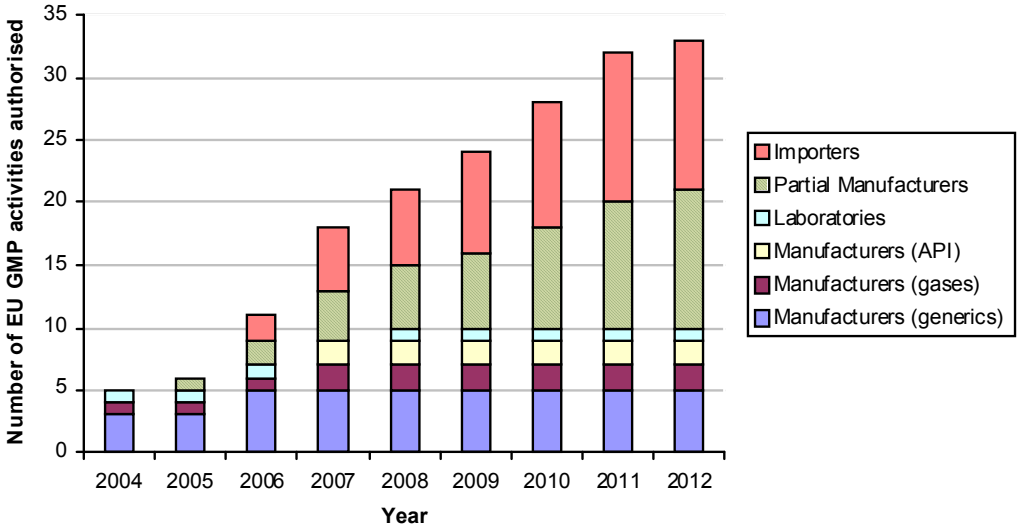


**Figure 10: Cumulative Number of EU GMP activities authorised**

There were four Inspections Review Group meetings held throughout 2012 where eight (8) cases related to GMP issues were discussed and decided upon.

## 6.3 Authorisations for wholesale dealing

During 2012 the Medicines Authority has also fulfilled its GDP inspection plan where twenty seven (27) GDP inspections were carried out. During 2012 eight (8) applications for new wholesale dealing licences were submitted. One of these one (1) was eventually withdrawn; four (4) applications were inspected and eventually licensed, whilst the other three (3) are still being processed. Twenty (20) variation applications for wholesale dealing authorisations were processed in 2012, out of which six (6) required an inspection.

## 6.4 Clinical trials

During 2012, the Medicines Authority continued to carry out inspections of clinical trials against EU GCP guidelines, which type of inspections, were started off for the first time in 2009. Two (2) GCP inspections were conducted in 2012 from the twelve (12) approved clinical trials in 2011, based on a risk based approach as specified in a dedicated SOP for clinical trials inspections.

## 6.5 Pharmacovigilance Inspections

Pharmacovigilance (PhV) inspections started to be conducted for the first time in 2011. Two inspections were carried out for the national marketing authorisations for medicinal oxygen (which are the only two national marketing authorisations). The Pharmacovigilance inspections were carried out against the national and EU legislation and the MA Pharmacovigilance obligations.

In 2012 one pharmacovigilance inspections were carried out for a national Marketing Authorisation Holder holding local marketing authorisations for products marketed locally, but with the main Pharmacovigilance Qualified Person (PhV QP) being located abroad at the corporate site.

For 2013 and 2014 it was agreed to carry out pharmacovigilance inspections for those products authorised locally with the obligation to implement risk minimisation measures (RMM plans) as a priority.

## 6.6 Pharmacies

Pharmacies are inspected on a two year cycle. During 2012 the Inspectorate and Enforcement Directorate (IED) started a new pharmacy inspections cycle after closing the previous 2010-2011 cycle in 2011. Therefore between 2010 and 2011 all the community retail pharmacies were inspected for the second time on a two year cycle started off in 2008. During 2012 IED carried out a total of one hundred and ten (110) retail community pharmacy inspections.

There were another six (6) pharmacy inspections following variation applications for pharmacy premises transfers or alterations which were carried out, whilst nine (9) administrative variations for pharmacy licences were processed.

In 2012 there were also four inspections for already existing Government entities' pharmacies. Two were renewal licence inspections for which the respective licences were renewed, whilst two other inspections were to issue for the first time a pharmacy licence. In the private hospital sector there were another three (3) pharmacy inspections for the renewal of the pharmacy licence of three private hospital in-patients pharmacies.

## 6.7 Granting of Qualified Person Status

In 2012 the Medicines Authority received nine (9) new applications for the Qualified Person (QP) status. Nine applicants were interviewed during 2012 and of these seven new QPs were approved.

## 6.8 Certificates of Pharmaceutical Products (CPPs)

During 2012, two hundred and twelve (212) CPPs were issued.

# 7.0 Regulation of medicinal products on the market and their use

## 7.1 Borderline Classification Committee

In 2012, twenty four (24) requests were received for the classification of 'borderline' products. Nineteen (19) of these products were classified as non-medicinal products.

## 7.2 Traditional Herbal Medicinal Products and Homeopathic Products

During 2012, a number of internal meetings regarding the implementation of the Traditional Herbal Medicinal Product Directive (THMP) (Directive 2004/24/EC amending Directive 2001/83/EC) were held. These followed on from meetings in previous years with the Licensing Authority and with other authorities and bodies, including with Malta Competition and Consumer Affairs Authority, Environmental Health Directorate and Port Health regarding the way forward on implementation of this legislation.

The focus of the meetings held during 2012 was the classification of further products from the information received from stakeholders. Following on from 2011, classification of almost all requests was made. Of the products received, more than 90% have been classified as non-medicinal and the companies have been informed. Applications for classification continue to be received. No applications for the registration of traditional herbal medicinal products have been received in 2012.

### Homeopathic products

No applications for the registration of homeopathic medicinal products have been received to date. The information session on herbal medicinal products will also focus on the need for registration of homeopathic medicinal products.

## 7.3 Advertising of Medicinal Products and Promotional Material

The Medicines Authority (MA) monitors the advertising of medicinal products and the issue of any promotional material related to such products and as being presented either to the public or to healthcare professionals. There is self-regulation in this area. Monitoring and assessment of medicinal product advertising typically extends over the major media formats, namely local newspapers and/or journals, local electronic medical journals and local television or radio broadcasts. Control of promotional material such as the provision of medicinal product samples to healthcare professionals and the sponsoring of promotional activities or scientific congresses is also regularly undertaken. Advertising and promotional material regulatory control is implemented according to the criteria set out within the Medicinal Products (Advertising) Regulations (L.N. 380 of 2005).

To a lesser degree, control of advertising material is also implemented via the ad hoc selection and investigation of local advertisements as presented within the major media formats. This activity principally aims at ensuring public health protection via the affirmation that the applicable legislation is consistently being upheld and rigorously adhered to.

Monitoring is mainly implemented via the application (in accordance with European legislation) of a self-regulatory approach whereby medicinal product advertising complaints as reported by external stakeholders are assessed and investigated in detail for purposes of verifying claims of breaches to the Advertising Regulations. During 2012, two (2) advertising complaints were registered with the Medicines Authority. All advertising complaints were dealt with within 2012.

## 7.4 Availability and Rational Use of Medicinal Products

The rational use of medicines is supported through the continuous update of the Medicines Authority website which is used by stakeholders as a source of independent information on medicines contributing to information and education about medicines. The Medicines Authority gave input into the National Guidelines for the use of Medicines and other relevant guidelines being prepared by the Superintendence of Public Health.

During 2012, the Availability of Medicinal Products Working Group was set up, with the initial remit to study the list of products authorised to be placed on the market in Malta and to establish which

therapeutic areas are not covered. The remit will be extended to liaise directly with the marketing authorisation holders or their representatives such that the Medicines Authority gets information on the marketing status of authorised medicinal products. It is planned that this information is made available to prescribers and patients. Companies will be involved in this exercise.

The Medicines Authority participated in the Medical School Conference and also presented a poster on the benefit risk assessment of medicines and new pharmaceutical legislation. Articles on both journals targeting healthcare professionals and magazines targeting consumers where published and the Authority actively participated in a number of media programmes targeted to the general public.

# 8.0 Surveillance of the local market

## 8.1 Rapid Alerts, GMP Non Compliance Notifications and Batch Defect Report

In this reporting period the Medicines Authority received one hundred and five (105) rapid alerts and nineteen (19) GMP non compliance notifications, which were investigated and out of which seven (7) resulted in recall of medicinal products from the local market.

## 8.2 Sampling of Medicines

The sampling plan for 2011 was closed positively and testing certificates issued by the contract lab were received for all samples. The sampling plan for 2012 was executed and all samples were sent abroad to the contract laboratory for analysis. The sampling plan included forty eight (48) medicinal products picked upon a risk based approach from community pharmacies for the national products market surveillance, and two (2) EU Centrally Authorised Products for the European surveillance plan.

# 9.0 Enforcement of Legislation

During 2012, the Medicines Authority carried out eight (8) investigations related to complaints and enforcement. The Enforcement Committee (a specific committee which discusses enforcement cases, chaired by the Licensing Authority) met once during 2012.

The Inspectorate and Enforcement Director attended seven (7) court sitting sessions during 2012 to provide court witness services. Five (5) case sittings concerned pharmacy issues and two sitting sessions concerned an enforcement case. Medicines Inspectors attended eight (8) court sessions regarded enforcement as witnesses.

## 10.0 Conclusion

During 2012, the Medicines Authority continued making a contribution to protect and enhance public health both in Malta and the EU. Three hundred and seventy four (374) medicinal products were authorised, and the Authority continued to contribute to the European network as a Reference Member State and as a Rapporteur for centralised procedures. The Medicines Authority processed one hundred and fifty three (153) Individual Case Summary Reports detailing three hundred (300) individual adverse drug reactions. Inspections of pharmaceutical activities continued to be held for Good Manufacturing Practice, Good Distribution Practice, Good Clinical Practice and pharmacovigilance. The milestones set by the corporate calendar were followed and achieved. New legislation on Pharmacovigilance and Falsified Medicines were transposed into National legislation and the employees of the Medicines Authority represented the Ministry on discussions regarding the review of legislation on clinical trials and further improvements on the Pharmacovigilance legislation.

The Medicines Authority looks forward to continue to consolidate its functions and responsibilities as the National Competent Authority for the regulation of medicinal product and pharmaceutical activities in Malta and at Europe level through the transparent and consistent execution of its regulatory role, this to the benefit of public health.