2013

Annual Report

AWTORITÀ DWAR IL-MEDIĊINI

Medicines Authority
203,Level 3,
Rue D'Argens,
Gzira,GZR 1363
Tel: (+356) 2343 9000
Fax: (+356) 2343 9161
Email: info.medicinesauthority@gov.mt

Review by the Chairperson

I am pleased to write this first review as the head of the Malta Medicines Authority, a focused and independent public entity committed to protect and enhance public health through the regulation of medicinal products and pharmaceutical activities.

As regulator, the Medicines Authority is making an impact on people's quality of life. Through our assessment, recommendations for authorisations and ongoing safety monitoring, we ensure that only products with a favourable benefit/risk profile are authorised to be placed on the market. During 2013, the Authority recommended six hundred ninety two (692) medicinal products for authorisation/ licensing leading to an overall increase of over six percent (6%) in the number of authorised products. It processed three thousand one hundred and sixty seven (3167) post authorisation procedures which include variations to market authorisations, transfers, renewals, notifications and withdrawals. The Authority fully transposed European legislation to enhance the safety of medicines (Directive 2012/26/EU), started involvement in an EU funded project to enhance its pharmacovigilance systems and enhanced rational use of medicines through regular independent information on medicinal products.

During 2013, the Authority actively supported the Department of Health to optimise the timely, equitable and affordable access to medicinal products. It has improved its communication with stakeholder through ongoing communication to better understand their needs and expectations and where possible translate into tangible initiatives. Pharmaceutical activities were regulated and supported with two hundred and fourteen (214) inspections and the issuance of two hundred and seventy five (275) certificates of pharmaceutical product which is important to facilitate the export of medicinal products.

The Authority focused on improving the quality of its output and upon my appointment, we immediately started the process to get certification for ISO 9001. A positive opinion was received by the certification body.

We are committed to move the Medicines Authority forward through a programme focused on two main pillars:

1) Regulating effectively and proportionally through a skilled workforce, good governance and an approach which listens and supports innovation,

2) Improving the Medicines Authority sustainability through the introduction of cost saving initiatives, revision of the fee structure and generation of new revenue.

I look forward to work with all stakeholders to protect and enhance public health.

Anthony Serracino Inglott

CONTENTS

1.0 Organisation

1.1 Leadership and Management

During 2013, 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, and performance appraisals for employees. Fifteen (15) Management and two (2) Interface meetings were held.

1.2 Customer Satisfaction and Communication with Stakeholders

In 2013, the Medicines Authority engaged into a number of proactive initiatives to enhance communication with stakeholders and customer satisfaction. A stakeholder satisfaction survey was carried out and following the survey, the Medicines Authority will take the following initiatives:

- To introduce a new service of fast track authorisation procedures for applications in line with Article 126a or Directive 2001/83/EC in line with a new proposal for the revision of licensing fees of the Medicines Authority.
- Promotion of electronic submission of applications through a Common EU Submission Portal.
- Updating of authorised products on website
- Implementation of a New Licensing System based on the result of the tender which is currently being adjudicated.

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 2013, three (3) complaints files regarding pharmaceutical activities were opened. Two complaints were closed by end of the year and one was ongoing as on 31st December 2013.

1.3 Quality Management

The year 2013 was a challenging year for the Quality Management Unit which was involved two key activities, namely, the third Benchmarking of European Medicines Agencies (BEMA III) and ISO 9001:2008 certification.

The overall objective of the BEMA exercise is mainly to rate the Medicines Authority against set key performance indicators for European medicines agencies and to identify a number of strengths / best practices and a number of opportunities for improvement. These enable the agency to act on opportunities for quality improvement specific to the agency. Furthermore, the results are shared anonymously across the network and act as a learning tool for all agencies whilst opportunities for improvement which are common across the agencies are identified and considered by the Heads of Medicines Agencies to provide the required support in addressing these gaps. In preparation for the BEMA visit a number of self-assessment reports were completed against targets for BEMA III. The actual on-site assessment at the Medicines Authority was carried out in April 2013. A number of strengths / best practices and opportunities for improvement were identified by the external assessors. The report was completed by the external assessors by end of May 2013. The Quality Manager also had the opportunity to present the setting up of a three-year audit strategy at the Working Group of Heads of Medicines Agencies for Quality Managers. The Medicines Authority is also in the process of addressing the opportunities for improvement identified with the aim of achieving quality improvement.

The ISO 9001:2008 Stage 1 certification audit was performed in October 2013 and Stage 2 certification audit was completed in December 2013. A positive recommendation for certification was received from the external auditor. The Medicines Authority is now expecting to obtain ISO certification in early 2014. The Quality Management Unit processed a total of 13 policies (8 of which were new policies). Fifty two (52) 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 self-assessment of the Benchmarking of European Medicines Agencies (BEMA) and also from new Pharmacovigilance legislation. It also aimed to streamline a number of processes mainly related to licensing activities. Moreover the review incorporated changes in policies as well as corrective and preventive action identified through implementation of operations, internal audits and Management Review.

The Quality Management Unit implemented the audit programme for 2013 in line with the three-year audit strategy. A total of eighteen (18) internal audits were performed in 2013 on the internal processes which resulted in a number of corrective and preventive actions.

A total of sixty seven (67) corrective actions and eighty two (82) quality improvements were processed by the Quality Management Unit. These relate to internal operations and resulted in the setting up / review of policies, standard operating procedures and amendments to standard documentation with the aim of continuously improving the internal operations towards increasing effectiveness and efficiency of its internal operations. 60% of the quality improvements identified resulted from internal / external audits. The implementation of all corrective and preventive actions is monitored by the Quality Manager.

An annual Management Review was performed in August – September 2013, 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

1.4 Human Resources Management

The number of persons employed by the Authority at the end of 2013 was 36 (2012: 36).

	2013 Female	2013 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 2013

Training and development priorities for 2013 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. During 2013, the Medicines Authority introduced teleworking as a family friendly measure.

Three staff meetings were held during 2013. 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 2013 the Information Systems Department continued to operate and maintain the core and European information systems and ICT infrastructure.

In March the Authority launched a new website which includes a new graphic design and advanced features which allow the Authority to more easily communicate with stakeholders. Development of a new online medicines database has also commenced which is expected to go live in 2014. This module will allow patients, health care professionals and other stakeholders to search for details of medicinal products using various keywords including the patient information leaflet and summary of product characteristics.

In February a tender for a new Licensing Management Solution was issued. Adjudication for the tender continued till the end of the year. The scope of the tender is to implement a solution that facilitates the interaction with its stakeholders, and improve back-office processes that include a case management system with document and workflow management capabilities. Through this implementation, the Authority aims to improve its business operations, facilitate operational efficiency, increase quality, and improve flexibility and processing lead times.

A contract was signed with the Irish Medicines Board to enroll in the Common EU Submission Portal (CESP). The latter is an online portal being developed by Member States (spearheaded by Ireland) which allows pharmaceutical companies to submit applications to national competent authorities electronically. An applicant company submits an application once to the portal and all concerned member states receive it automatically. The benefit of the project is that companies save on the large amount of paper used to send the scientific dossiers of medicinal products and courier charges. This initiative also allows Malta to reduce the administrative burden on the private sector.

A PC backup solution was installed on all PCs to automate the task of backing up local data to an external device. The data is encrypted before saved to the external drive for maximum security. In the future the current solution will be replaced by a cloud service.

The Medicines Authority has carried out extensive testing on its system which will lead to the migration of a new office suit in 2014. To continue the trend towards reducing paper usage and enhance user experience, three additional employees were provided with dual TFT screens.

1.6 Collaboration with other Entities

During 2013, 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.

2.0 Regulatory Affairs

2.1 Participation in drafting new legislation

The Medicines Authority continued to participate on behalf of the Ministry on the 'Clinical Trials regulation' proposed by the Commission, by attending meetings held under the Council and drawing up reports and instruction notes for these meetings on the Proposal for a Regulation of the European Parliament and of the Council repealing Directive 2001/20/EC as to clinical trials. The Authority also participated in the discussions on a Commission proposal for a Directive of the European Parliament and of the Council amending, as regards fees for pharmacovigilance activities.

2.2 Update and Implementation of legislation

During 2013, the Medicines Authority supported the Licensing Authority in the transposition process of Directive 2012/26/EU. The following Legal Notices were published:

L.N. 352 of 2013. Pharmacovigilance Regulations, 2013
L.N. 351 of 2013. Medicinal Products (Labelling and Packaging) (Amendment) Regulations, 2013
L.N. 349 of 2013. Medicines (Marketing Authorisation) (Amendment) Regulations, 2013
L.N. 350 of 2013. Wholesale Distribution and Brokering of Medicinal products and Active Substances (amendment) Regulations, 2013;

3.0 Assessment and Authorisation of Medicinal Products

During 2013, the Medicines Authority continued with activities towards national and European procedures. The number of authorised medicinal products in Malta (excluding products authorised through the centralised procedure) as on 31st December 2013 was four thousand five hundred and thirty six (4536) (see Figure 1 for route of authorisation).

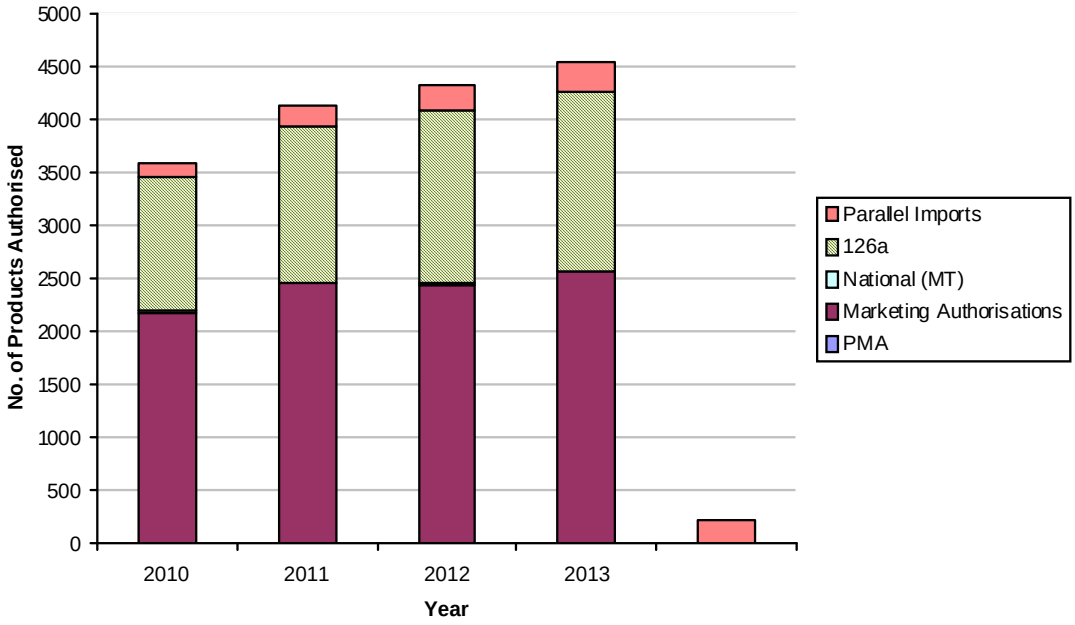


Figure 1 – Cumulative Number of Authorised Medicinal Products in Malta (excluding products authorised through the centralised procedure) as on 31st December 2013

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 (e.g. CHMP, CMDh, PRAC and working parties), where relevant and discussion on any guidelines that have an impact on the procedures discussed in the Committee. Issues relating to the local market, such as safety issues following on from European referrals are discussed. Meetings are held on a monthly basis.

3.2 European Procedures

3.2.1 Marketing Authorisation Procedures

Malta as rapporteur in the Centralised Procedure

During 2013, Malta was rapporteur for two (2) new centralised procedures (5 marketing authorisations) and also for variations for previous products for which Malta was rapporteur through the centralised procedure. Malta continues to bid for rapporteurships of centralised procedures on a monthly basis. During 2013, Malta was also the rapporteur for one (1) 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 five (5). A total of sixteen marketing authorisations were granted in 2013 for European procedures received through the Mutual recognition and Decentralised with Malta as RMS. Some of the procedures started in 2013 are currently still ongoing.

Applications for abridged applications were assessed for oral dosage forms, injectable preparations 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 with the aim of widening the scope for participation in European procedures. Additional training, particularly in terms of quality assessment, in collaboration with another competent authority is planned for 2014.

Figures 2 and 3 show the number of finalised and started MRP/ DCP Procedures within the EU in 2013, including Malta (MT). None of the procedures for which Malta was Reference Member State were

referred to the Coordination Group for the Mutual Recognition and Decentralised Procedures (CMDh) and were concluded positively and within the stipulated timelines.

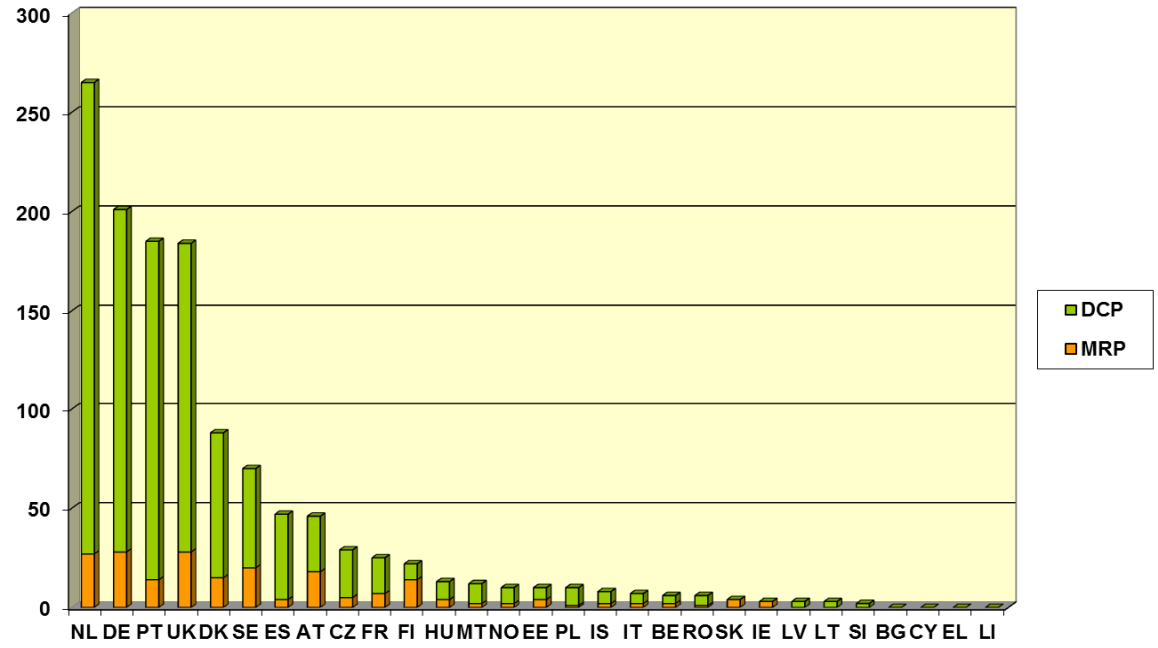


Figure 2 –Finalised MRP/ DCP Procedures within the EU in 2013

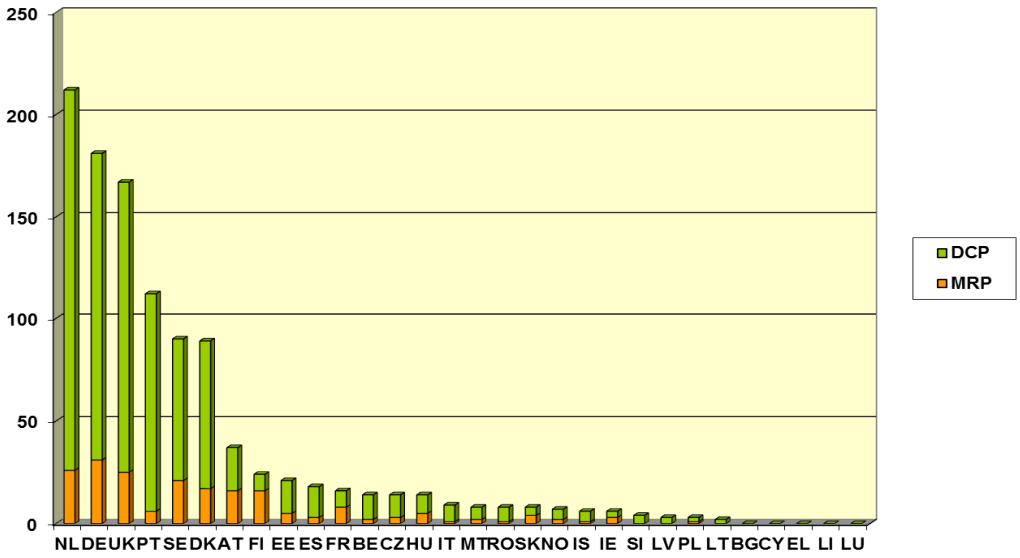


Figure 3 – Started MRP/DCP Procedures within the EU in 2013

Post-authorisation procedures

The number of variations for products where Malta is RMS received was eighty eight (88).

For procedures for which Malta is Reference Member State, team meetings are organised for each procedure 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 presented at the Medicines Review Committee, in particular where technical or regulatory decisions have to be taken or endorsed for a final Malta position.

The Medicines Authority continues to strive to continue to participate actively in European procedures as a Reference Member State/ Rapporteur and the fees for Reference Member State activities were reduced in line with the demand for the activity.

Malta as Concerned Member State

Two hundred and seventeen (217) European marketing authorisation product applications were received in 2013 with Malta as Concerned Member State. Forty three (43) were received through the Mutual

Recognition Procedure (MRP) and one hundred and seventy four (174) through the Decentralised Procedure. This is similar to trends in other European countries, where MR procedures are declining as companies make more use of the DC procedure. The number of marketing authorisations granted for the two types of procedures for the same period was fifty one (51) and two hundred and twenty four (224) respectively (Figure 4). Compared to 2012, the number of Decentralised and Mutual Recognition procedures with Malta as Concerned Member State decreased by 16%, following the same trend of fewer procedures being submitted at European level.

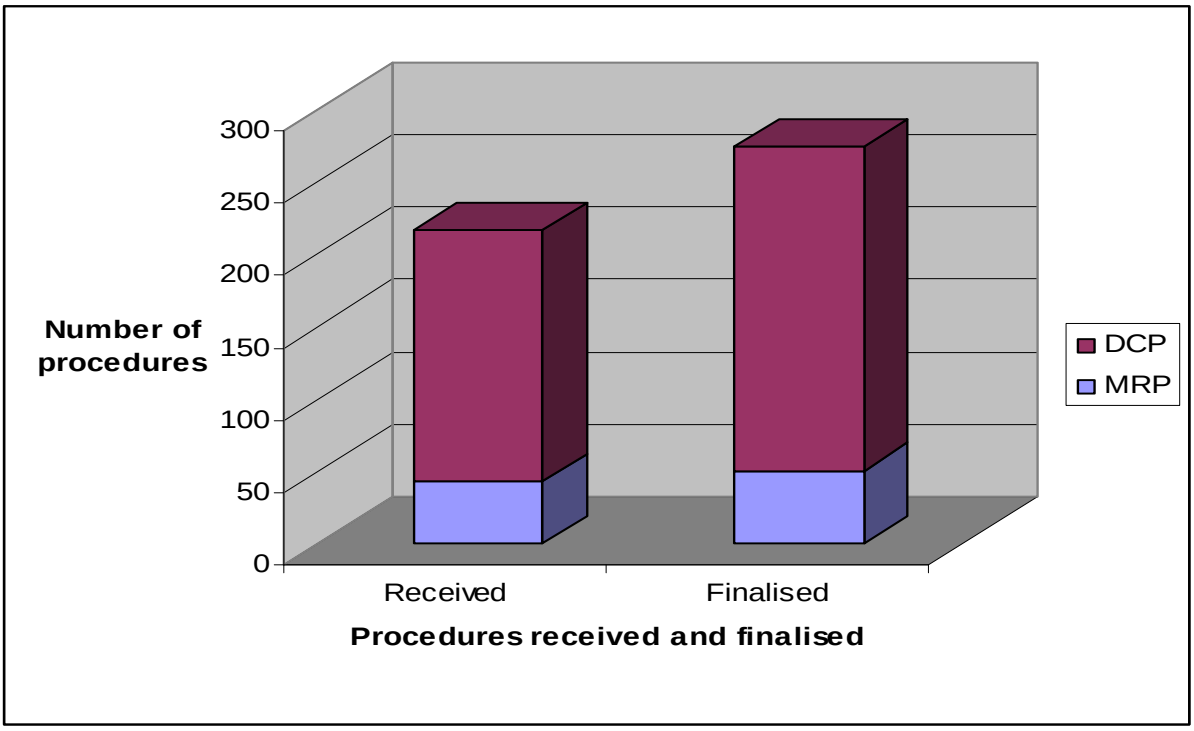


Figure 4: Applications received and finalised for MR and DC procedures with Malta as Concerned Member State in 2013

The Licensing directorate improved its output and timelines for the finalisation of the national phase for European procedures and almost all marketing authorisations for procedures finalised in 2013 were issued within the 30-day timeline. Most of the pending procedures from the previous 2 years (also due to the lack of submission of required documentation by applicants) were also finalised.

European post-authorisation procedures

One thousand two hundred and ninety three (1293) Mutual Recognition Procedure variation applications were received in 2013 and one thousand two hundred ninety four (1294) were finalised. These include ongoing procedures from 2012. One hundred and thirty seven (137) renewal applications were received and sixty six (66) were finalised. Twenty six (26) article 61(3) notifications were received and twenty two (22) were finalised during 2013 (Figure 5). Fifty requests for the withdrawal of marketing authorisations granted through MR and DC procedures were received.

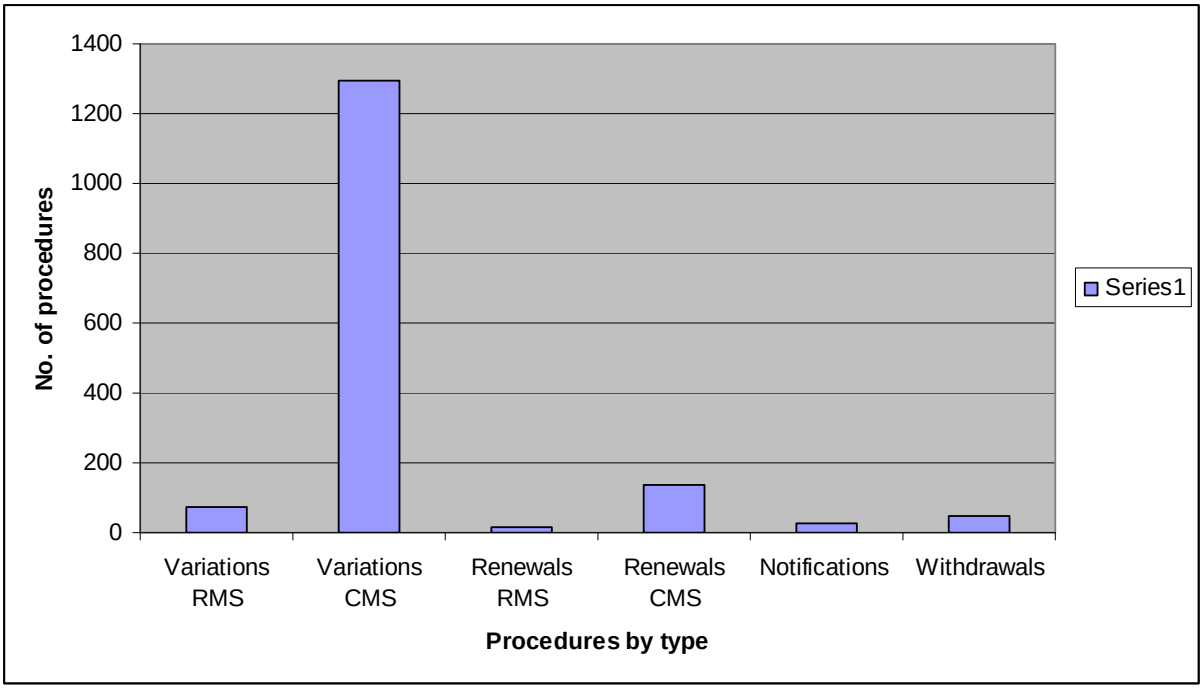


Figure 5 - Summary of post-authorisation procedures received through the European Procedures (MRP) in 2013 – MT CMS

3.2.2 Work-sharing Procedures

During 2013, the Medicines Authority representatives at the Paediatric Committee (PDCO) at the European Agency in London were involved as rapporteurs or peer reviewers for decisions in paediatric investigation plans. As at end 2013, MT was involved during 2013 in nine (9) PDCO procedures.

3.3 National Procedures

National marketing authorisation applications

A total of fourteen (14) national marketing authorisation applications were received in 2013, mainly line extensions to nationally authorised products. Ten procedures (10) were finalised in the same period.

Parallel import applications

Sixty eight (68) parallel import licence applications were received and sixty four (64) finalised by the end of 2013. 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 2013 was three hundred and three (303) and two hundred and thirty seven (237) authorisations were issued in the same period. A summary of the national authorisation procedures received and finalised in 2013 is given in Figure 6.

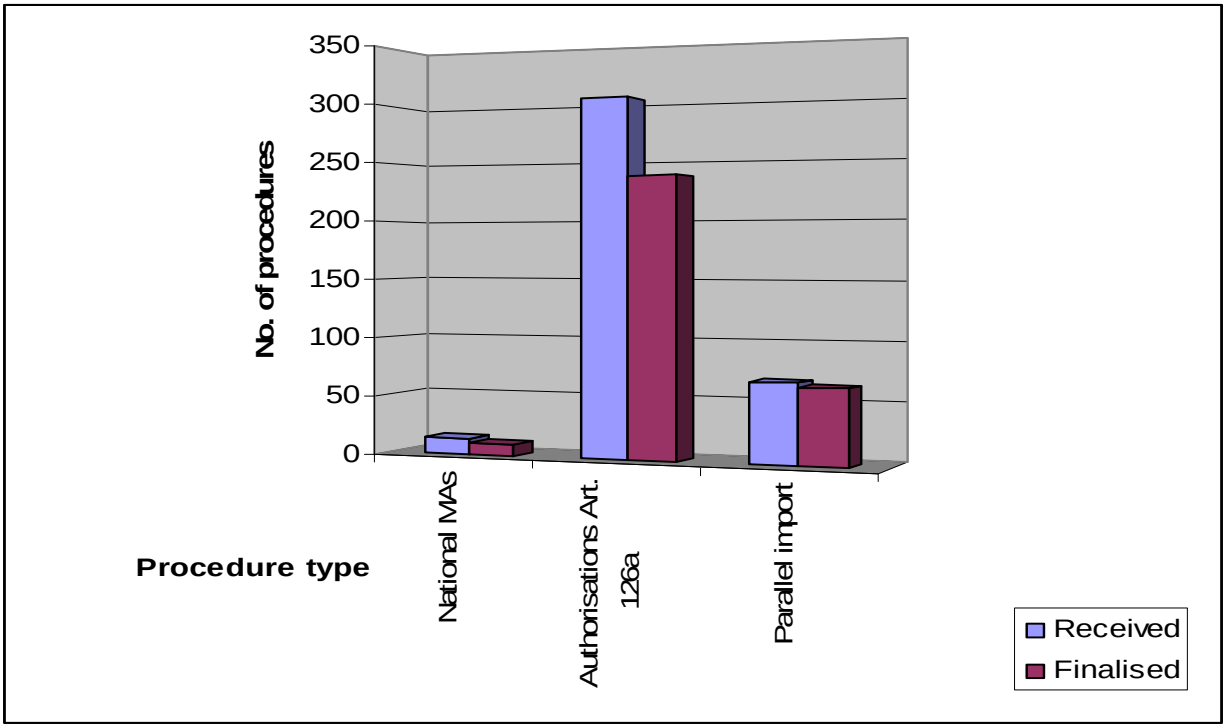


Figure 6 - Summary of national procedures received and finalised in 2012. Some procedures were continued from previous years.

National variation applications

Eight hundred and eighty nine (889) national variation applications were received in 2013. One thousand four hundred and fifty two (1452) procedures were finalised. National variations received with payment (not with an approval from another Member State) were prioritised for assessment during 2013 and pending variations from the previous year were also concluded.

National notification 61(3) applications

Sixty nine (69) national article 61(3) notifications were received. One hundred and fifty (150) procedures were finalised with updates to the product information.

National renewals

Thirteen (13) national renewal applications were received and sixty five (65) were finalised in 2013.

Transfer of marketing authorisations

Seventy one (71) applications for the transfer of a marketing authorisation holder were received and sixty six (66) processed.

Withdrawals of marketing authorisations and licences

Applications for the withdrawal of national marketing authorisations received totalled one hundred and sixteen (116), fifty two (52) withdrawals for authorisations in accordance with article 126a and three (3) parallel import licences.

Summary

A summary of the national procedures received and finalised in 2013 is given in Figure 7.

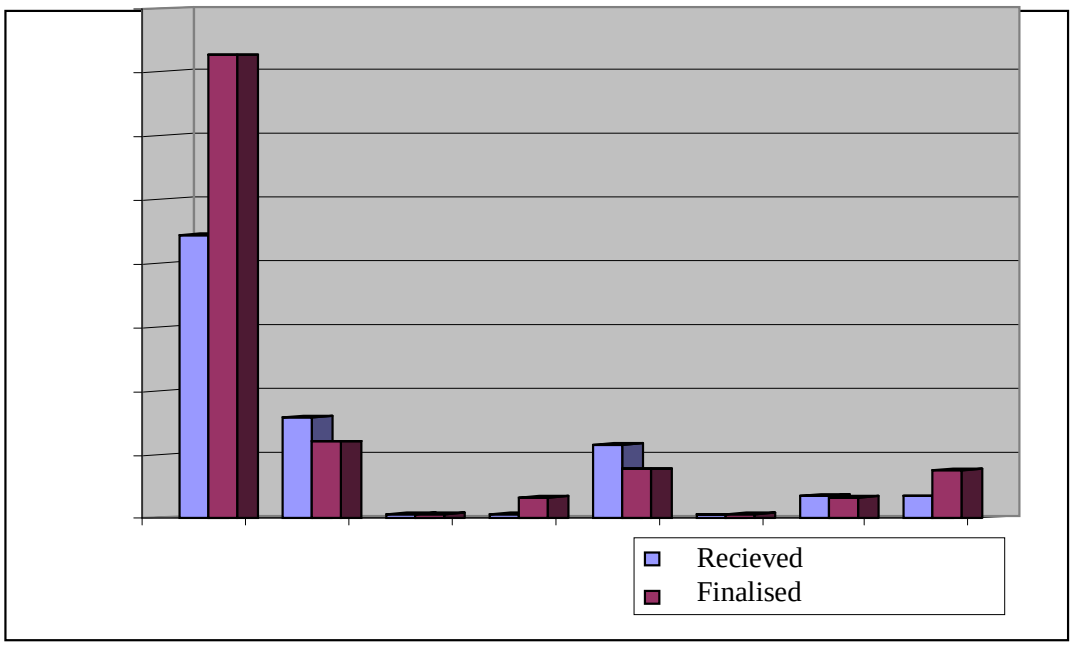


Figure 7 – Summary of national post-authorisation procedures received and finalised in 2013

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

In 2013, 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. The product information in the Maltese language 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 2013, One (1) scientific advice request has been submitted to the Medicines Authority. The procedure was finalised in 2013.

4.0 Clinical Trials

During 2013, One (1) Clinical Trial application was submitted to the Medicines Authority. This was a patient registry (and does not fall under 2001/20/EC rules and obligations). Three (3) amendments to trials which are being conducted in Malta were received. All amendments were approved in 2013. 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, 2012 and then again in 2013.

5.0 Pharmacovigilance

Safety of medicines is a priority area for the Medicines Authority and the Authority will continue to strengthen its efforts to ensure the safe use of medicinal products on the local market. 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 its 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 conditions of marketing authorisations from marketing authorisation holders as well the approval of Direct Healthcare Professional Communications informing of key messages to prescribers and suppliers of medicinal products for human use. 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 at 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 (150) Individual Case Summary Reports (ICSRs) were registered over 2013. Each of these cases detailed at least one adverse drug reaction to the medicinal product concerned thus resulting in a total of three hundred (349) individual adverse drug reactions. Figure 8 gives a breakdown of these adverse drug reactions according to system organ classification. Each case report received at the Medicines Authority was assessed 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 9 and 10 further classify the adverse drug reaction case reports (as received over 2013) 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 2013, 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 8 Distribution of Adverse Drug Reactions according to System Organ Classification in 2013

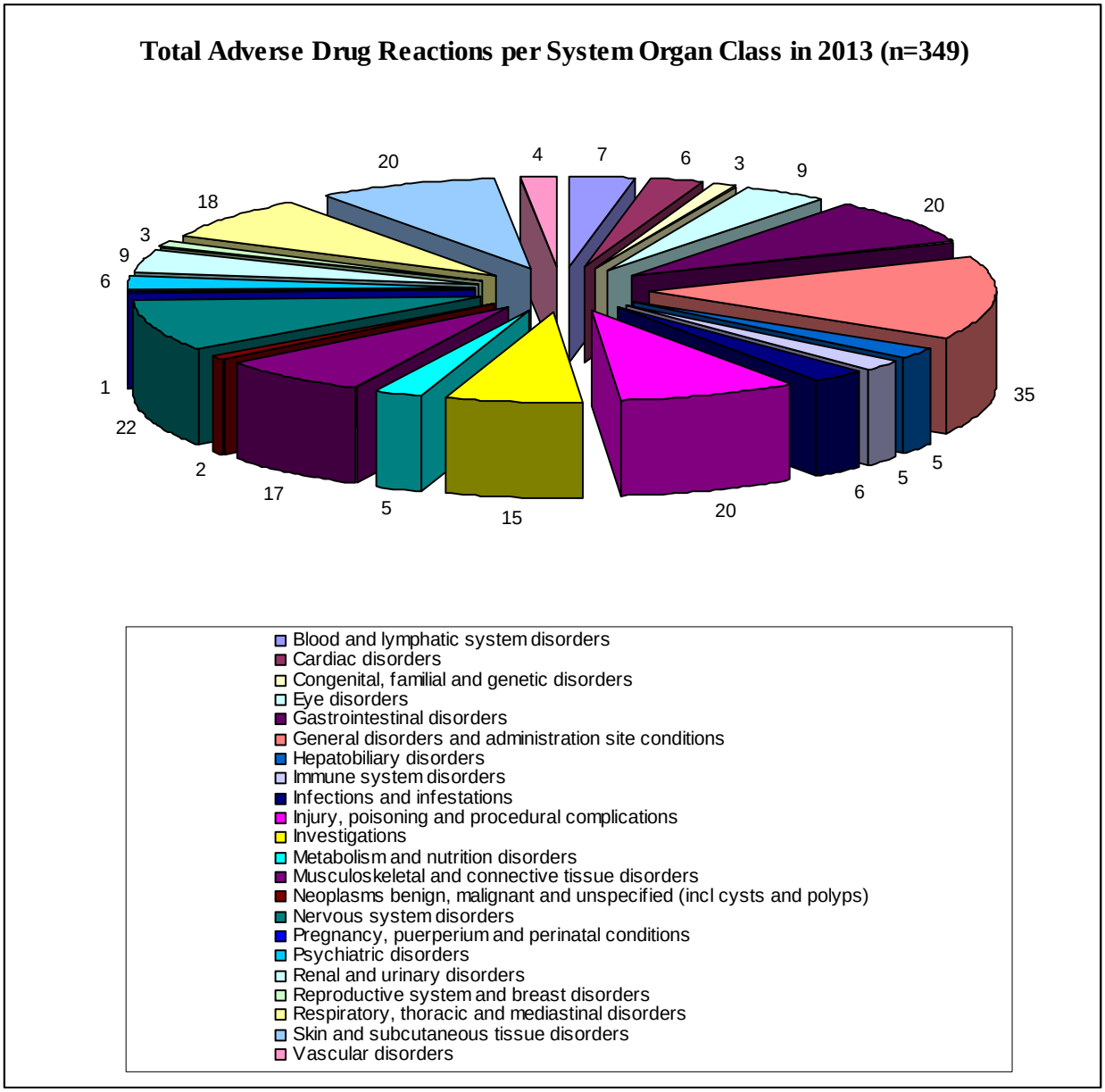


Figure 9 Frequency of ICSRs according to seriousness in 2013 (n=150)

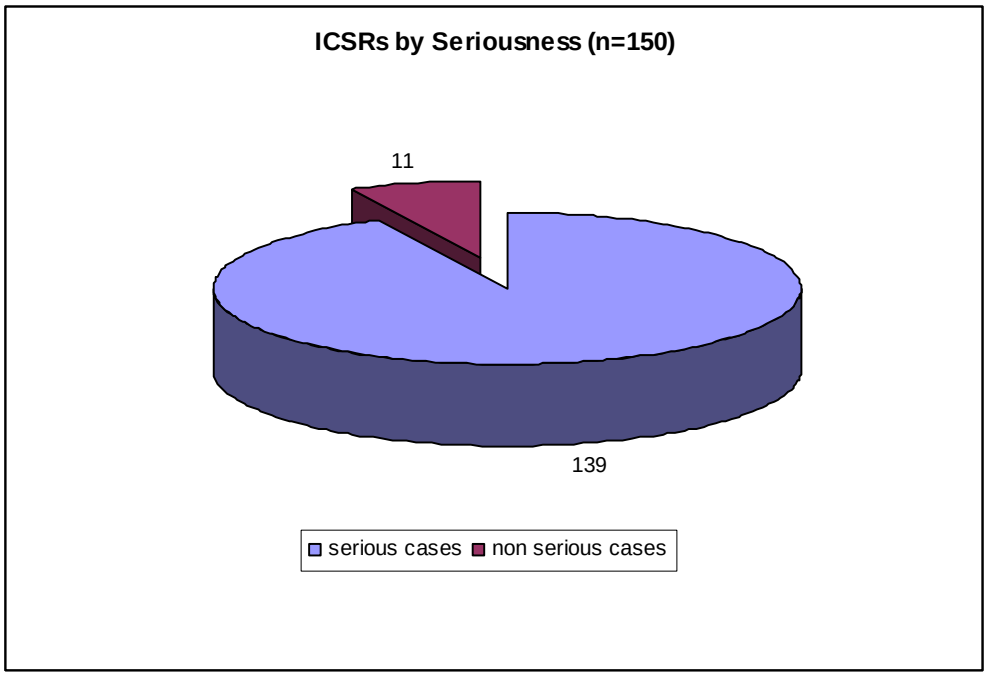
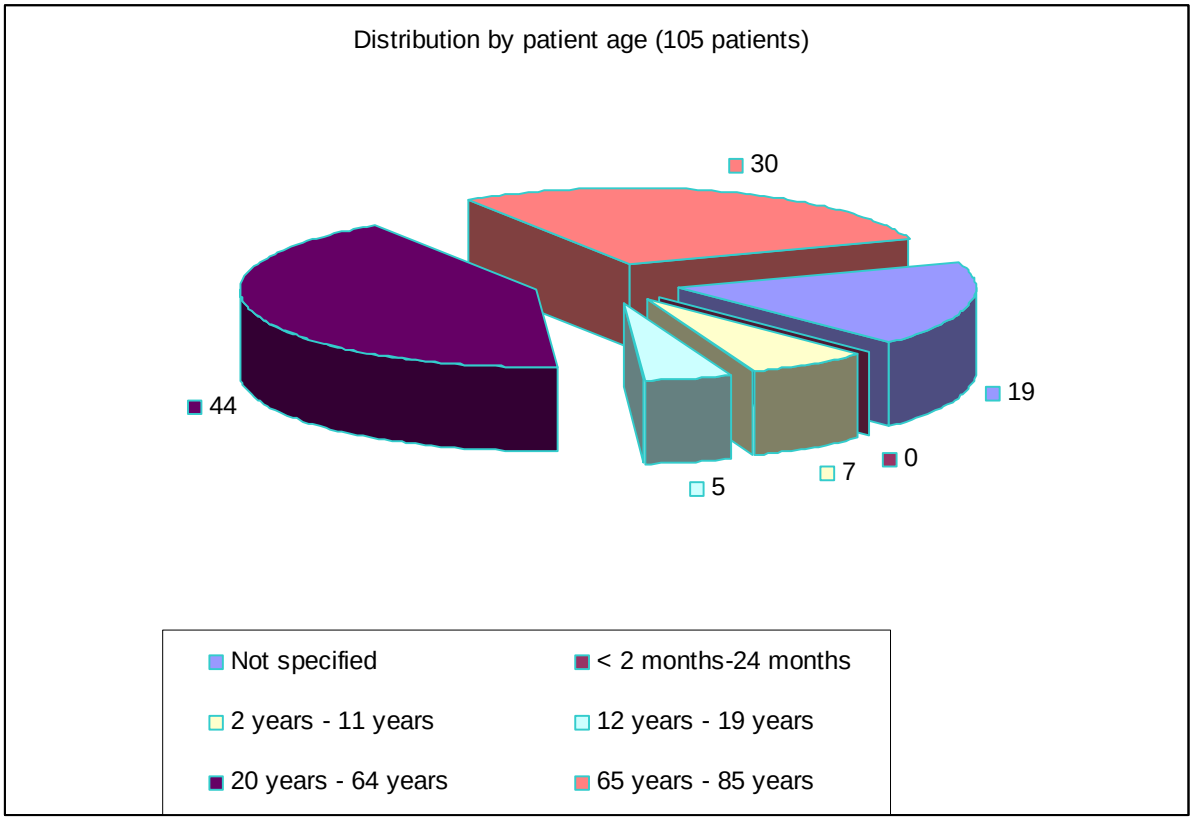


Figure 10 Percentage distribution of case safety reports according to patient age 2013


Distribution by patient age (105 patients)
30
19
0
7
5
44
Not specified
< 2 months-24 months
2 years - 11 years
12 years - 19 years
20 years - 64 years
65 years - 85 years

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.

Several activities are undertaken by the Medicines Authority for purposes of attaining effective product safety surveillance, amongst which are the (1) approval of Direct Healthcare Professional Communications (DHPCs) detailing safety/risk changes to scientific information and recommendations on product administration methods; (2) investigation of newly identified safety signals with immediate product suspension and/or recall as relevant (Safety Signal Investigations, Rapid Alerts and Product Safety Recalls); (3) approval and monitoring of Pregnancy Prevention Programmes as proposed in relation to potentially teratogenic medicinal products; (4) monitoring of risk minimisation programmes relating to high risk medicinal products and provision of the relevant regulatory information in order to establish such programmes; (5) issue of Safety Circulars and Media Statements addressed to healthcare professionals and the general public respectively. These documents normally give recommendations on medicinal product use and applicable cautionary and precautionary measures. Throughout 2013 the Medicines Authority continued implementing the SMS notification service whereby subscribed medical and healthcare professionals can receive alerts and links to the safety circulars as soon as they are published on the website. (6) Communication as relevant with the Department of Healthcare Services Standards on toxicological risks identified in relation to blood products (Haemovigilance); (7) Initiation and subsequent approval of variations to scientific medicinal product information relating to identified novel or increased risk (Urgent Safety Restrictions); (9) 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). (10) Review of newly emergent data concerning safety evidence of a medicinal product, substance or class upon request. (11) 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 2013.

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.

Table 2: Pharmacovigilance and safety issue reviews and communications – 2013

Documents Received	Number of submissions
PSURs	1106
Risk Management Plans	93
SUSAR	4
Annual Reassesments	36
Direct Healthcare Professional Communications	40
Safety Circulars	28
Other Circulars	1
Risk minimisation measures	110
Rapid Alert	5
Non Urgent Information	15

Table 3: Pharmacovigilance related queries in 2013 (n=92)

ADRs	Query	Number
	Testing requirements	2
	Request for acknowledgments	1
	Literature report requirements	5
	ICSR reporting requirements for Malta	10
	Feedback on new ADR form	1
PSURs	PSUR submission requirements after publication of 2010/84/EU	12
	Request for acknowledgment of PSUR receipt	2
Clinical Trials	SUSARs/DSURs/LineListings	7
Pharmacovigilance legislation	National requirements for ADR submission, status of national legislation, request for guidelines	9

	EU-QPPV or Drug safety responsible requirements	4
	Pharmacovigilance product information text on that should be implemented in SmPC and PIL	8
Other	Requirements for submission of Risk Minimisation Measure	8
	Requirements for submission of DHCPs	3
	Student projects	7
	Named patient basis/Compassionate use programmes	4
	XEVMPD	1
	Medical devices	1
	Off-label use	1
	Requirements for Advertisement of Medicinal Products	3
	Newspaper Report	1
	Access to Medicine Data	1
	Samples	1

5.2 New Pharmacovigilance Procedures by the Medicines Authority

In 2013, the Medicines Authority transposed Directive 2012/26/EU and continued implementing commission implementing regulation 520/2012 on Pharmacovigilance. To achieve these objectives Standard operating procedures on safety recalls and crisis management became effective in 2013 as well as a work instruction on signal detection. This year was also a year in which all pharmaociviglance processes were audited in line with the standards set by commission implementing regulation 520/2012. The results of the pharmacovigilance audit were submitted to the EU commission.

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 and 2013. Table 4 shows the number of authorised pharmaceutical activities in Malta.

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
GMP authorised sites	5	6	11	18	21	24	28	32	3333	
Wholesale Dealers	82	74	66	69	74	72	71	71	7072	
Community Pharmacies	208	206	207	207	208	209	211	215	219220	

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.

One Good Clinical Practice (GCP) inspections was identified based on a risk based approach, carried out and successfully concluded in 2013. For the third year, the Medicines Authority also continued with its Pharmacovigilance inspections in its annual inspection plan. Six (6) Pharmacogivilance inspections were carried out in 2013 for products with Risk Minimisation Measures.

6.1 Participation of Inspectors in international fora

During 2013, 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 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 delegated and implementing acts to be issued under Directive 2011/62/EU, the Falsified Medicines Directive amending Directive 2001/83/EC.

6.2 Manufacturing and Importation Authorisations (MIAs)

During 2013 the Medicines Authority carried out twenty seven (27) GMP inspections for new, renewal or follow up of GMP licences/certificates as follows, out of which there were one new application for Active Substances.

Three (3) for an active pharmaceutical ingredient and four (4) for non sterile solid dose manufacturers; two (2) for medicinal gases manufacturers; one (1) contract laboratory inspection for its GMP certificate renewal; seven (7) inspections for MAs for repackaging and re-labelling / partial manufacturing operations; ten (10) inspections for MAs of importation activity: five (5) from countries which have Mutual Recognition Agreements (MRAs) with the EU for GMP and five (5) from countries which do not have an MRA.

Apart from these the Blood Establishment inspection was carried out in 2013 as well as the Mater Dei Pharmacy inspection with its additional unit. The Authority, in line with the new requirements brought

about by the implementation of the Falsified Medicines Directive (Directive 2011/62/EU), received applications, inspected and registered the following entities: three (3) API importers and distributors and two (2) brokers of finished dosage forms.

A total of twenty one (21) MAs administrative variation applications were processed in 2013 for manufacturers and importers. Cumulative number of EU GMP authorised activities is shown is Figure 10.

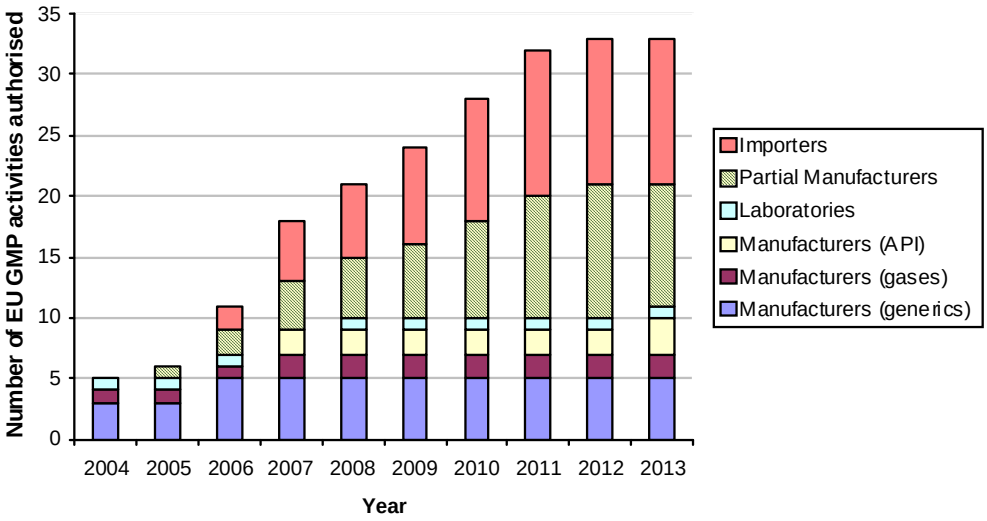


Figure 10: Cumulative Number of EU GMP activities authorised

There were six Inspections Review Group meetings held throughout 2013 where seven (7) cases related to GMP and GDP issues were discussed and decided upon in nine discussion sessions.

6.3 Authorisations for wholesale dealing

During 2013 the Medicines Authority has also fulfilled its GDP inspection plan where fifty one (51) GDP inspections were carried out. During 2013 three (3) applications for new wholesale dealing licences were submitted. The three (3) applications were inspected and eventually one (1) licensed, whilst the other two (2) are still being processed. Twenty eight (28) variation applications for wholesale dealing authorisations were processed in 2013, out of which five (5) required an inspection.

6.4 Clinical trials

During 2013, 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. One (1) GCP inspection was conducted in 2013, 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 was 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. In 2013 six such pharmacovigilance inspections were carried out.

6.6 Pharmacies

Pharmacies are inspected on a two year cycle. During 2013 the Inspectorate and Enforcement Directorate (IED) closed off the pharmacy inspections cycle started in 2012, after closing the previous 2010-2011 cycle in 2011. Therefore between 2012 and 2013 all the community retail pharmacies were inspected for the third time on a two year cycle started off in 2008. During 2013 IED carried out a total of one hundred and five (105) retail community pharmacy inspections.

There were another five (5) pharmacy inspections following variation applications for pharmacy premises transfers or alterations which were carried out, whilst forty nine (49) administrative variations for pharmacy licences were processed.

In 2013 there were also four inspections for already existing Government entities' pharmacies to renew their licences. Twelve (12) applications for a new pharmacy licence were received, out of which two could be considered for processing in line with the legal requirements.

6.7 Granting of Qualified Person Status

In 2013 the Medicines Authority received thirteen (13) new applications for the Qualified Person (QP) status. Eleven applicants were interviewed during 2013 and of these ten new QPs were approved. Four applicants who submitted their applications at end of 2012 were also interviewed in 2013 and all four passed. Therefore in 2013 a total of 14 new QPs were approved.

6.8 Certificates of Pharmaceutical Products (CPPs)

During 2013, two hundred and seventy five (275) CPP applications were received out of which two hundred and seventy two CPPs were issued.

7.0 Regulation of medicinal products on the market and their use

7.1 Borderline Classification Committee

The borderline classification committee classifies products into medicinal products and non-medicinal products when requests for classification are received from companies and from other sources. In 2013, sixty one (61) requests were received for the classification of 'borderline' products. The classification is based on the definition of a medicinal product but other criteria are also taken into consideration such as the classification in other Member States. Other bodies, such as the Malta Consumer and Competition Affairs Authority and Port Health are also involved in 'borderline' product issues and this collaboration enables better information sharing on these products until final classification.

7.2 Traditional Herbal Medicinal Products and Homeopathic Products

No applications for the registration of traditional herbal medicinal products have been received in 2013.

Homeopathic products

No applications for the registration of homeopathic medicinal products have been received to date.

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 (LN. 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. Over 2013 two (2) advertising complaints were registered with the Medicines Authority. All advertising complaints were dealt with within 2013.

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.

During 2013, the Availability of Medicinal Products Working Group continued its work on the identification of therapeutic gaps in terms of availability of authorised medicinal products. 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 and their collaboration is very important.

In 2013, the Availability Working group started a new project – that of identifying any discrepancies in the legal classification of authorised medicinal products as granted to date (and as requested by the applicants). This is being done with the intention of harmonising products with a prescription only and

those with a non-prescription status. The therapeutic areas to be prioritised in 2014 will be the analgesics, anti-inflammatory and antirheumatic products and topical preparations.

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 sixty four (164) rapid alerts and GMP non compliance notifications, which were investigated and out of which fourteen (14) resulted in recall of medicinal products from the local market and one in a cautionary use letter.

8.2 Sampling of Medicines

The sampling plan for 2012 was closed positively and testing certificates issued by the contract lab were received for all samples. The sampling plan for 2013 was executed and all samples were sent abroad to the contract laboratory for analysis. The sampling plan included a number of samples from eight (8) different types of medicinal products picked upon a risk based approach from CPSU, mostly from the Marsa Stores, whilst there were no EU Centrally Authorised Products for the European surveillance plan under EDQM for 2013.

9.0 Enforcement of Legislation

During 2013, the Medicines Authority worked upon nine enforcement cases / investigations out of which five (5) new cases opened in 2013 were related to complaints and enforcement. There was no need for the Enforcement Committee (a specific committee which discusses enforcement cases, chaired by the Licensing Authority) to meet during 2013.

The Inspectorate and Enforcement Director attended seven (7) court sitting sessions during 2013 to provide court witness services. Five (5) case sittings concerned pharmacy issues and two sitting sessions concerned an enforcement case. Medicines Inspectors attended eleven (11) court sessions regarded enforcement as witnesses.