

# PHARMACEUTICAL ACTIVITIES AND THEIR REGULATION

TONIO CASSAR B.Pharm.(Hons.)  
DIRECTOR INSPECTORATE AND ENFORCEMENT  
MEDICINES AUTHORITY  
MALTA



# AGENDA

- Introduction
- Topics to be covered
- Legislation, Regulations , Standards
- Responsibilities
- The Medicines Authority
- Administrative Issues
- Discussion



# INTRODUCTION

- Pharmaceutical activities cover products through clinical trials, manufacture, wholesale dealing and dispensing.
- The scope of legislation is to ensure the quality, safety and efficacy of medicines and thus public health.

# TOPICS

- Manufacture and Importation
- Wholesale dealing
- Parallel importation
- Clinical trails
- Advertising (7<sup>th</sup> March session)
- Pharmacies (31<sup>st</sup> January session)





# LEGISLATION

## MANUFACTURE AND IMPORTATION

- Medicines Act, Act III of 2003 Part III Title II which came fully into force on 1/12/03.
- L.N. 381 of 2005 – Manufacture and Importation Regulations.
- L.N. 485 of 2004 – GMP regulations.

# LEGISLATION cont.

- EC Directive 2001/83 as amended by 2004/27 (*requirement for API`s to be manufactured to GMP*).
- EC Directive 2003/94 – Principles and Guidelines of GMP for Medicinal Products and Investigational Medicinal Products.

# LEGISLATION cont.

## WHOLESALE DEALING

- Medicines Act, Act III of 2003 Part III Title III which came fully into force on 1/12/03.
- L.N. 386 of 2005 – Wholesale Distribution Regulations.
- EC Directive 2001/83 as amended by 2004/27.

# LEGISLATION cont.

## PARALLEL IMPORTATION

- L.N. 437 of 2004 – Parallel Importation Regulations.

## CLINICAL TRIALS

- L.N. 490 of 2004 – Clinical Trial Regulations.

# LEGISLATION cont.

## PHARMACY

- Medicines Act, Act III of 2003 Part III Title IV which came fully into force on 1/12/03.
- L.N. 31 of 1984 – Dispensaries (Licensing) Regulations.

# LEGISLATION cont.

## ADVERTISING

- L.N. 380 of 2005 – Medicinal Products (Advertising) Regulations.

## LABELLING AND PACKAGING

- L.N. 393 of 2005 – Medicinal Products (Labeling and Packaging) Regulations.

# MANUFACTURE AND IMPORT REGULATIONS

- A manufacturing licence is required to manufacture medicinal products (Med. Act art. 37, L.N. 381 of 2005 art. 3 (1a)).
- Products covered – industrially produced medicinal products, homeopathic, herbal, investigational medicinal products, medicinal products derived from human blood, radiopharmaceuticals.

# MANUFACTURE AND IMPORT REGULATIONS cont.

- Licence is required for total (finished product) and partial manufacture (bulk product), assembly, packaging and change in presentation to packs (Med. Act art. 37, L.N. 381 of 2005 art. 3 (2a)).

# MANUFACTURE AND IMPORT REGULATIONS cont.

- Licence is also required for re-packaging:
  - Removal of blister packs from original external pack and placing into new pack.
  - De-blistering and re-blistering.
  - Insertion/change of patient information leaflet.
  - Fixing of labels/stickers to outer/inner pack.

(Med. Act art. 37, L.N. 381 of 2005 art. 3 (2a)).



# MANUFACTURE AND IMPORT REGULATIONS cont.

- Licence is required for products intended for the local market and also for those for export only (L.N. 381 of 2005 art. 3 (1b)).
- Licence is also required for the importation of products from outside the EU (L.N. 381 of 2005 art. 3 (3)).

# MANUFACTURE AND IMPORT REGULATIONS cont.

- Such licence is also required for the re-export to third countries of imported products, even if such products are untouched (EC Directive 2001/83 art. 40).
- A manufacturing licence authorises the manufacturer to distribute his products by wholesale (L.N. 381 of 2005 art. 3 (4)).

# MANUFACTURE AND IMPORT REGULATIONS cont.

- A licence shall apply only to premises, medicinal products and dosage forms as specified in the application (L.N. 381 of 2005 art. 5 (2)).
- Licences are valid for 2 years.
- Licensing Authority may suspend, revoke or vary a licence (Med. Act art. 40, 41).

# MANUFACTURE AND IMPORT REGULATIONS cont.

- A manufacturing licence is not required for the preparation, dividing up, changes in packaging or presentation of products if this activity is carried out by a pharmacist in a licensed pharmacy for individual patients (Med. Act art. 37, L.N. 381 of 2005 art. 3 (2b)).

# MANUFACTURE AND IMPORT STANDARDS cont.

- EU GMP principles and guidelines (Part I and II + annexes) in respect of premises, equipment, control facilities and personnel must be complied with (L.N. 381 of 2005 art. 4, 7 (1)), L.N. 485 of 2004 art. 4 (3)).
- Qualified Person must be available (L.N. 381 of 2005 art. 4 (c)).

# MANUFACTURE AND IMPORT STANDARDS cont.

- QP`s shall possess a science degree at university level (4 year course) and have at least 2 years of practical experience in the manufacture of medicinal products (L.N. 381 of 2005 art. 9).

# MANUFACTURE AND IMPORT ROLE OF LICENCE HOLDER

- Comply with EU GMP principles and guidelines (L.N. 381 of 2005 art. 7 (1)).
- Inform the Licensing Authority (LA) of any change in QP (Med. Act art. 44 (a)).
- Inform LA of any change in premises, processes, products and personnel (Med. Act art. 44 (f)).

# MANUFACTURE AND IMPORT ROLE OF LICENCE HOLDER cont.

- Enable the QP to perform his duties (Med. Act art. 44 (c)).
- Maintain records (Med. Act art. 44 (d)).
- Employ adequate personnel and train them accordingly (Med. Act art. 44 (e)).
- Provide access to inspectors of the MA to premises (Med. Act art. 44 (b)).

# ROLE OF THE QUALIFIED PERSON

- Concept of the QP was established in 1975 and applies within EU only.
- The QP is responsible to ensure that the manufacture of medicines is properly controlled.
- Pharmacists are ideally suited to perform the duties of a QP (*if fulfilling the required conditions of practical experience*).

# ROLE OF THE QUALIFIED PERSON cont.

- Ensure EU GMP standards at all times (Med. Act art. 45 (1a)).
- Ensure that each batch has been manufactured, tested and complies in all respects with the provisions of the Medicines Act and the Marketing Authorisation (Med. Act art. 45 (1b)).

# ROLE OF THE QUALIFIED PERSON cont.

- Ensure in the case of imported products that each batch has undergone a full qualitative and quantitative analysis within the EU (L.N. 381 of 2005 art. 11(b)).
- Such controls are not needed for those products coming from Canada, Australia, NZ, Switzerland - the manufacturers' batch certificates can be used (EU MRA) (L.N. 381 of 2005 art. 11(2)).



# ROLE OF THE QUALIFIED PERSON cont.

- A QP must keep a register and certify (sign) that each batch satisfies the legal provisions and the required standards. This is a legal responsibility (L.N. 381 of 2005 art. 12 (1)).
- QP is responsible for release (authorise for sale and use) of products, this responsibility cannot be delegated.
- Licensing Authority may suspend a QP in cases on non-compliance or misconduct (Med Act art. 46).



# WHOLESALE DEALING REGULATIONS

- A wholesale dealing licence is required to engage in wholesale dealing of medicinal products (Med. Act art. 54 (1), L.N. 386 of 2005 art. 4).
- The licence covers the distribution and storage activities for products within the EU.
- For narcotics and psychotropics an additional authorisation is required on the licence.

# WHOLESALE DEALING REGULATIONS cont.

- The licence entitles the holder to export products.
- Medicinal products to be placed on the Maltese market must possess a Market Authorisation (Med. Act art. 54 (1)).
- The Market Authorisation must be issued by the Medicines Authority or by the EMEA for centralised products (L.N. 386 of 2005 art. 3).

# WHOLESALE DEALING REGULATIONS cont.

- For products of EU origin that are stored but not distributed in Malta only the WL is required and a Marketing Authorisation is not required (L.N. 386 of 2005 art. 3).
- A licence shall apply only to premises, dosage forms and activities as specified in the application (Med. Act art. 56 (2), L.N. 386 of 2005 art. 6 (2), 7).

# WHOLESALE DEALING REGULATIONS cont.

- Licences are valid for 2 years.
- Licensing Authority may suspend, revoke or vary a licence (Med. Act art. 57, 61).

# WHOLESALE DEALING REGULATIONS cont.

- Wholesale dealers shall:
  - Obtain supplies from
    - Licensed manufacturers (Malta/EU).
    - Licensed wholesale dealers (Malta/EU).
  - Supply products to:
    - Other licensed wholesale dealers (Malta/EU/3<sup>rd</sup> countries).
    - Licenced pharmacies (L.N. 386 of 2005 art. 7 (2b,c)).



# WHOLESALE DEALING REGULATIONS cont.

- Cannot sell directly to doctors (agreement reached on 10/1/06 that doctors will need to order supplies through a pharmacy).
- Not purchase products from pharmacies of other EU member states for distribution in Malta. Once the product moves out of wholesale the chain is broken.



# WHOLESALE DEALING STANDARDS

- EU GDP guidelines in respect of premises, documentation, personnel, equipment deliveries, returns, self inspections must be complied with (L.N. 386 of 2005 art. 7 (2f)), EU guideline 94/C 63/03).
- Responsible person must be available for each wholesale dealer (Med. Act art. 55 (1e)).

# WHOLESALE DEALING STANDARDS cont.

- A responsible person must be a registered pharmacist (L.N. 386 of 2005 art. 2).
- He/she is the technical person responsible for storage and distribution activities.
- He/she has the authority and responsibility to implement and maintain a quality system.

# WHOLESALE DEALING ROLE OF LICENCE HOLDER

- Comply with EU GDP guidelines (L.N. 386 of 2005 art. 7 (2f)), EU guideline 94/C 63/03).
- Ensure suitable and adequate premises, installations and equipment to guarantee proper conservation and distribution (L.N. 386 of 2005 art. 7 (1a)).
- Employ adequate staff and provide them with training (L.N. 386 of 2005 art. 7 (1b)).



# WHOLESALE DEALING ROLE OF LICENCE HOLDER cont.

- Provide access to inspectors of the Medicines Authority (L.N. 386 of 2005 art. 7 (2a)).
- Keep records of transactions for a period of 5 years. Records shall include:
  - Date
  - Name and dosage form of product
  - Quantity received or supplied
  - Name and address of supplier or consignee (L.N. 386 of 2005 art. 7 (2e)).



# WHOLESALE DEALING

## ROLE OF LICENCE HOLDER cont.

- Provide an invoice of sale when supplying products and include the above mentioned details (L.N. 386 of 2005 art. 8 (1)).
- Ensure that an appropriate and continuous supply of products is available (L.N. 386 of 2005 art. 8 (3)).
- Inform the Medicines Authority of each product and batch he intends to place on the Maltese market (L.N. 386 of 2005 art. 3 (2)).

# WHOLESALE DEALING

## ROLE OF LICENCE HOLDER cont.

- Inform the Market Authorisation Holder (MAH) of each product he intends to place on the Maltese market (L.N. 386 of 2005 art. 3 (2)).
- Obtain a letter of access from the MAH and provide a copy to the Medicines Authority (L.N. 386 of 2005 art. 8 (2)).
- Have the services of a responsible person (Med. Act art. 55 (1e)).

# WHOLESALE DEALING ROLE OF LICENCE HOLDER cont.

- Has an emergency action plan to effectively recall any products from the market (L.N. 386 of 2005 art. 7 (2d)).
- Collaborate with the Medicines Authority and MAH in the implementation of batch recalls (L.N. 386 of 2005 art. 7 (2d)).

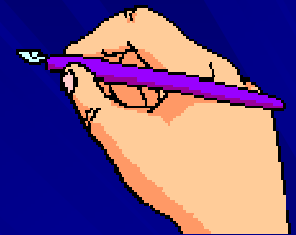
# WHOLESALE DEALING ROLE OF RESPONSIBLE PERSON

- Comply with EU GDP guidelines (L.N. 386 of 2005 art. 7 (2f)), EU guideline 94/C 63/03).
- Ensure that conditions for storage of products are in accordance with the market authorisation and labeling (L.N. 386 of 2005 art. 9(b)).



# WHOLESALE DEALING ROLE OF RESPONSIBLE PERSON cont.

- Monitor all areas used for storage and distribution (L.N. 386 of 2005 art. 9 (c)).
- Maintain records (L.N. 386 of 2005 art. 9 (d)).
- Ensure that a quality system is in place and maintained (L.N. 386 of 2005 art. 9 (e)).



# PARALLEL IMPORTATION

- What is parallel importation?
  - the importation into Malta from an EU country of a medicinal product which already has a market authorisation in Malta, and also in the source country, by someone other than the appointed representative of the market authorisation holder.

# PARALLEL IMPORTATION cont.

What is parallel distribution?

- This involves the same activity but involves centrally authorised products.

Why does parallel activity takes place?

- Because of price differences in medicinal products between different EU member states.



# PARALLEL IMPORTATION cont.



**PARALLEL ACTIVITY IS LEGAL  
AND CAN ONLY BE UNDERTAKEN  
BETWEEN EU MEMBER STATES**

# PARALLEL IMPORTATION LEGISLATION

- L.N. 437 of 2004 – Parallel Importation of Medicinal Products Regulations.
- COM (2003) 839 - Commission Communication on Parallel Imports.

# PARALLEL IMPORTATION REGULATIONS

- A parallel import licence is required for each product to be placed on the market (L.N. 437 of 2004 art. 3 (1)), *(list on website)*.
- A wholesale dealers licence is also required (L.N. 437 of 2004 art. 3 (2a)).
- A parallel import licence shall cease to be valid if the original marketing authorisation is withdrawn for public health reasons (L.N. 437 of 2004 art. 5 (2)).

# PARALLEL IMPORTATION STANDARDS

- The same standards and obligations as for wholesale dealing must be achieved.

# PARALLEL IMPORTATION

## ROLE OF LICENCE HOLDER

- Comply with EU GDP guidelines (L.N. 386 of 2005 art. 7 (2f)), EU guideline 94/C 63/03).
- Keep an audit trail of his supplies from the authorised distributor or manufacturer (L.N. 437 of 2004 art. 7 (a)).
- Follow pharmacovigilance issues with his supplier and Medicines Authority (L.N. 437 of 2004 art. 7 (b)).



# PARALLEL IMPORTATION

## ROLE OF LICENCE HOLDER cont.

- Keeps records of the origin, quantities and batch numbers of products (L.N. 437 of 2004 art. 8 (1)).
- If the product is repackaged ensure that this is done under GMP conditions, in a licensed manufacturing site and in accordance with a written contract (L.N. 381 of 2005 art. 3 (2a)).

# PARALLEL IMPORTATION

## ROLE OF LICENCE HOLDER cont.

- Notify the MAH and the Medicines Authority in cases where a parallel product is to be repackaged (L.N. 437 of 2004 art. 7 (c)).
- Ensure that the parallel import licence number is present on the outer pack (L.N. 437 of 2004 art. 7 (d)).



# RECALLS

## ■ Are classified as:

- Class I
  - life threatening.
  - immediate action.
- Class II
  - cause illness/mistreatment.
  - action in 48 hrs.
- Class III
  - no significant hazard.
  - action within 5 days.

# RECALLS cont.

- Cases or suspects of quality defects must be reported to the Medicines Authority.
- All reports are investigated.
- A decision can be taken to recall the product. This is usually done in agreement with the MAH.

# RECALLS cont.

- The RP and wholesaler are responsible to issue batch recall letters, manage and effect the recall according to its classification.
- Full reconciliation report must be submitted once the recall is finalised.

# CLINICAL TRIAL LEGISLATION

- L.N. 490 of 2004 – Clinical Trials Regulations.
- EC Directive 2001/20 – Implementation of GCP.
- EC Directive 2005/ 28 – Principles and Detailed Guidelines of GCP (*issued for consultation for transposition into national legislation*).

# CLINICAL TRIAL REGULATIONS

- All clinical trials, including bioavailability studies, shall be designed, conducted and reported in accordance with GCP principles (L.N. 490 of 2004 art. 2 (2)).
- Prior to initiation of a trial approval must be sought from:
  - Ethics committee
  - Medicines Authority(L.N. 490 of 2004 art. 7 (1), 9 (1,2)).



# CLINICAL TRIAL REGULATIONS

## cont.

- Investigational Medicinal Products (IMP) shall be manufactured in accordance with a manufacturing licence and GMP standards (L.N. 490 of 2004 art. 13 (1), L.N. 485 of 2004 art. 5).
- This applies also for IMP`s intended for export (L.N. 490 of 2004 art. 13 (1)).

# CLINICAL TRIAL REGULATIONS

## cont.

- An IMP is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial and includes products already with a marketing authorisation but used or assembled in a way different from the authorised form, or when used for an unauthorised indication or to gain further information about the authorised form.

L.N. 490 of 2004 art. 3).

# CLINICAL TRIAL REGULATIONS

## cont.

- The responsibilities of the QP are the same as for licenced medicines (L.N. 490 of 2004 art. 14).
- The packaging of IMP`s must comply with the requirements of annex 13 of the EU GMP guide (L.N. 490 of 2004 art. 15).

# CLINICAL TRIAL STANDARDS

- Guidance on GCP – ICH topic E 6 (adopted by EU).
- World Medical Association Declaration of Helsinki – Ethical principles for medical research involving human subjects 1996.

# CLINICAL TRIAL ROLES AND RESPONSIBILITIES

- The well being, rights, safety, privacy and dignity of patients must be protected.
- A protocol should be established to define the study.
- A written informed consent should be obtained from each patient prior to initiation of trial.
- IMP`s must be of GMP quality.

# CLINICAL TRIAL ROLES/RESPONSIBILITIES cont.

- Personnel must be fully trained.
- Monitoring of the trial must be done.
- All actions must be fully documented.
- Strict confidentiality must be kept.
- Authorisation must be obtained prior to initiation of trial.

# Pharmacies

- Another important activity at the end of the cycle is that relating to pharmacies. This topic has been extensively covered in the lecture of the 31/1/06.

# THE MEDICINES AUTHORITY

- Fully established in November 2003.
- The MA is empowered by the Medicines Act as the National Competent Authority to regulate pharmaceutical activities in Malta.

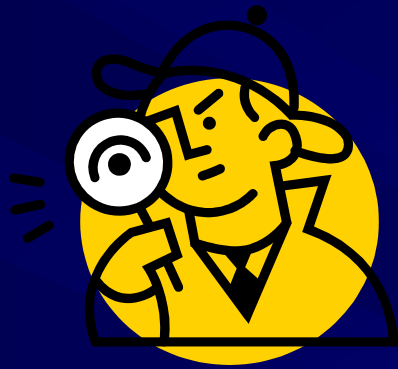
# THE MEDICINES AUTHORITY

## cont.

### Mission statement:

*to contribute to the protection of public health in Malta through the regulation of the safety, quality and efficacy of medicines for sale or supply on the Maltese market. The Authority is committed to providing high quality, licensing, monitoring and inspection services to customers, amongst whom are Ministers, the pharmaceutical industry and general public. As part of this commitment the Medicines Authority has implemented a system designated to manage quality in its operations and in its service to customers.*

(Medicines Authority Quality Manual)



# INSPECTIONS

THE AIM AND SCOPE OF  
INSPECTIONS IS TO ENSURE  
THAT COMPLIANCE IS ACHIEVED  
AND MAINTAINED.

COMPLIANCE SAFEGUARDS PATIENT  
SAFETY AND PUBLIC HEALTH

# INSPECTIONS cont.

WHAT IS EXPECTED ?

# INSPECTIONS cont.

- It is essential that:
  - A Quality System is in place.
  - Applicable standards are achieved.
  - Documentation is kept up to date.
  - Records are kept e.g. temperature, cleaning, pest control.
  - Monitoring is achieved.
  - Systems are under control.

# INSPECTIONS cont.

ALWAYS REMEMBER.....

**IF IT`S NOT WRITTEN,  
IT`S NOT DONE**

# CLASSIFICATION OF DEFICIENCIES

## ■ CRITICAL

- *A deficiency which has produced, or leads to a significant risk of producing, a product which is harmful to patients, or*
- *A combination of several major deficiencies which taken all together may represent a critical deficiency.*

# CLASSIFICATION OF DEFICIENCIES cont.

## ■ MAJOR

- *A non-critical deficiency which has produced, or may produce, a product which does not comply with its market authorisation and specifications.*
- *A deficiency which indicates a major variation from EU GMP, GDP, GCP principles.*
- *A combination of several other deficiencies which taken all together may represent a major deficiency.*

# CLASSIFICATION OF DEFICIENCIES cont.

## ■ MINOR

- *A deficiency which cannot be classified as critical or major but which indicates a departure from GMP, GDP, GCP principles.*

# INSPECTIONS

- Following an inspection the company is given time, depending on type of deficiencies found, to address issues and achieve compliance.
- Documentary evidence is required to ensure that shortcomings have been rectified.
- A follow-up inspection may be required.

# INSPECTIONS cont.

- Administrative action against the licence and/or licence holder and/or prosecution in court will be taken in cases of serious non-compliance.
- Case involving pharmacists will be reported to the Pharmacy Council for additional action to be considered.



# ADMINISTRATIVE ISSUES

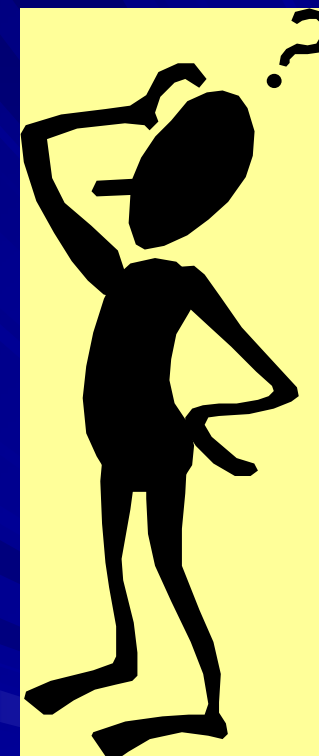
- A licence is required for all pharmaceutical activities.
- An application for variation of licence must be lodged for any change in licence e.g. change in licence holder, premises etc.
- MA to be informed in writing when responsible person changes.

# ADMINISTRATIVE ISSUES cont.

- QP`s must be approved by MA prior to being included on a manufacturing licence.
- MA to be informed in writing if QP or RP is temporarily substituted.
- Application forms for new licences or variations are available on the website.

# ADMINISTRATIVE ISSUES cont.

- If in doubt about something always contact the Medicines Authority and seek advice.



# THE CURRENT SCENARIO

- Locally there are 7 licenced manufacturers:
  - 2 solid dose full manufacture
  - 1 solid dose full manufacture (incl. IMP`s)
  - 1 medicinal gases manufacture
  - 1 liquid dose full manufacture
  - 1 homeopathic manufacture
  - 1 repackaging
  - other companies are being set up.

# THE CURRENT SCENARIO cont.

- At present there are 71 wholesalers, including 5 full-line (*i.e. purchase a wide range of supplies for re-distribution to pharmacies*).
- 3 companies are licensed as parallel importers.
- There is 1 ongoing clinical trial initiated after 1/5/04 according to EU requirements.

# CONCLUSION

- Responsibilities are various depending on the type of activity.
- It is important for pharmacists working in the various fields to be familiar with legislation, the requirements and standards to be achieved.
- The good of patients and securing public health are primary objectives of regulations.

# THANK YOU

[www.medicinesauthority.gov.mt](http://www.medicinesauthority.gov.mt)  
[inspectorate.adm@gov.mt](mailto:inspectorate.adm@gov.mt)

