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The role of the Biological Laboratory in the regulation of the quality of Biological Products

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Israeli Ministry of Health

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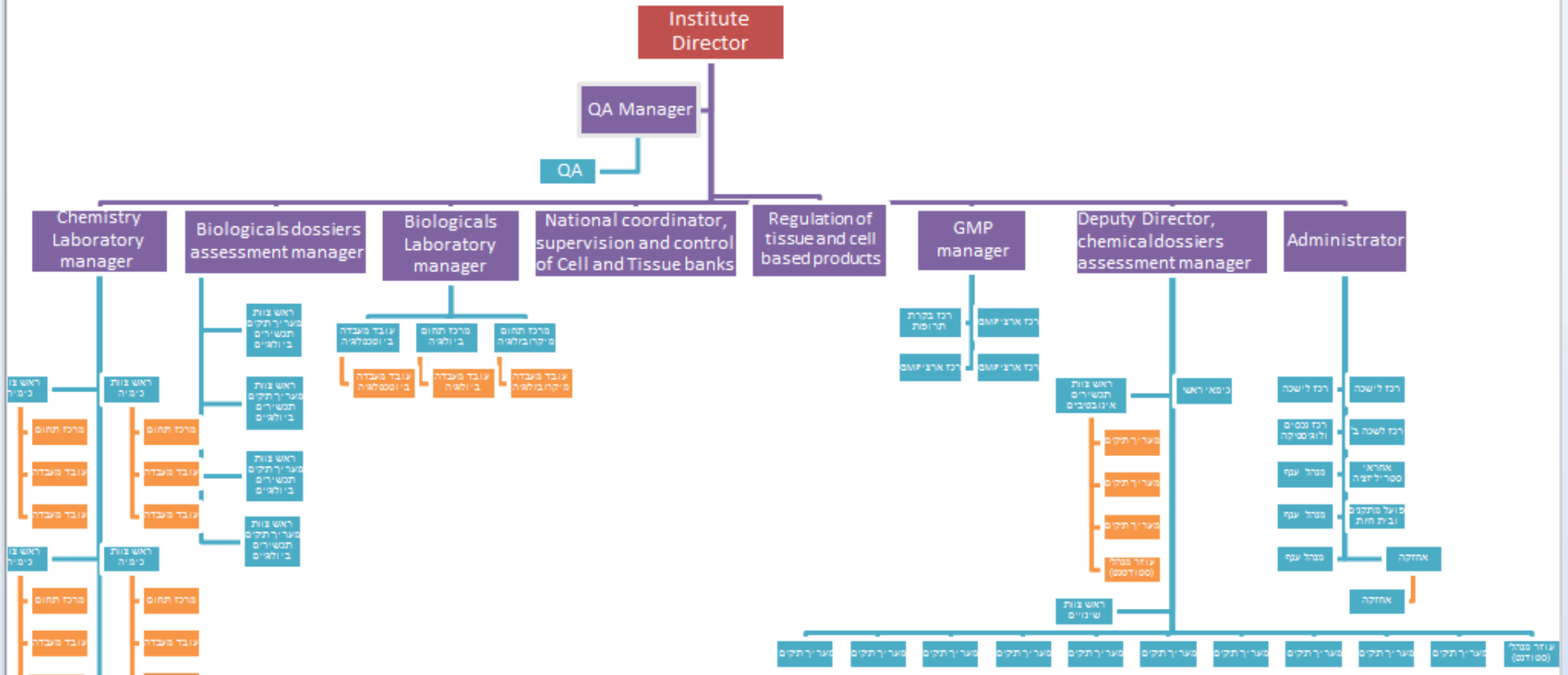
The Institute for Standardization and Control of Pharmaceuticals



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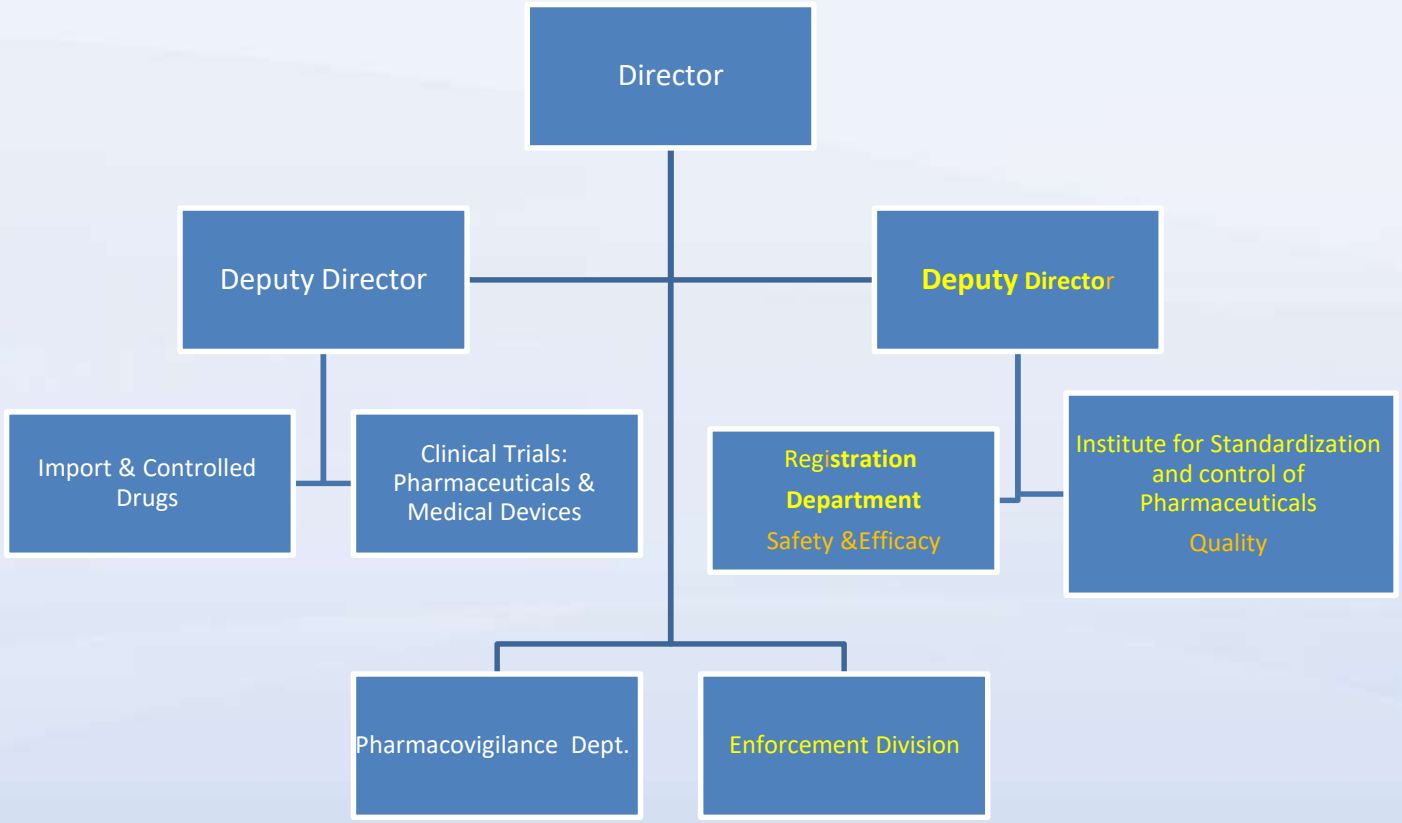
Center for pharmaceutical and Enforcement Divisions



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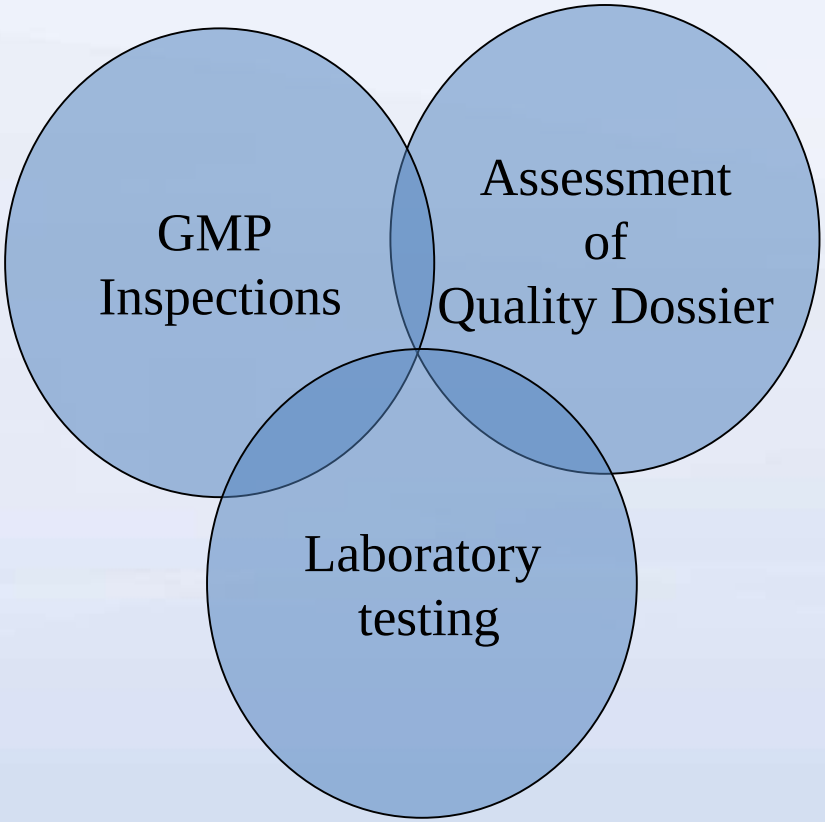
How do we regulate quality?



International Agreements(1)

- ACAA Agreement (Agreement on Conformity Assessment and Acceptance) approved in The European Parliament (01/2013)
- Mutual recognition on GMP and Laboratory Testing
  - Acceptance as an associate member of the general European OMCL network - 2/2014
  - Implementation of OCABR of blood products and Vaccines
  - Memorandum of Understanding with OCABR networking regarding participation in activities of OCABR networking for medicinal products derived from human blood and plasma.

International Agreements(2)

- Observers to European Pharmacopoeia
  - Observers to Group 6B of the European Pharmacopoeia
  - Confidentiality Agreement with EDQM regarding CEP
- Member of PIC/S
- MOU with FDA, Swiss Medic
- Participation in the DMF assessment for UNICEF in the prequalification program

Structure and Personnel

- The biological Laboratory conducts biochemical/Immunochemical methods. (SEC-HPLC , Clottable protein, Electrophoresis by Agarose gel and SDS-PAGE, Coagulation Assays etc.). (4 analysts)

- The Microbiology Laboratory conducts MLT ,Sterility, Endotoxin and Activity of Antibiotics. (2 analysts)

Types of Activities

- Pre-Marketing Testing of Biological Products.
  - New Registration of Immunoglobulin and biosimilar, first batch of product.
- Post-Marketing Surveillance of Biological Products.
  - Risk based assessment of biological products, Renewal after 5/10 years for all Biological products
- Official Control Authority Batch Release (OCABR).
  - Since 2014 , after the ACAA agreement between EU and Israel , the laboratory tests each of blood products, outside the EU according to the OMCL guidelines
  - . All the vaccines are released according to their manufacturing protocols, and a certificate from a western country
- Pharmaceutical preparations, complaints, cosmetics
  - Those products are tested mainly for microbiology purity
- Development of new methods (including validation and guidelines).

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Post-Marketing

Different types of risks are incorporated in the PM program:

1.Risk connected to the raw material: origin, stability, solubility, complicated manufacturing process, novelty of the active substance, multiple API manufacturers of a single medicinal product.

2.Risk coming from the final product: pharmacological class subjected to non-conformities, product likely to be falsified, very low frequency of production, new production processes, new ingredient combinations, new formulations, narrow therapeutic windows, new manufacturing sites, low doses of API.

3. Risk associated with target populations: vulnerable populations suffering from severe disease

4. Regulatory environment : batch release performed by national authority or not, coordinated program of MS, new version of monographs, market withdrawals, pharmaceutical questions raised during the marketing authorization process.

5.Pharmacovigilance- therapeutic class with frequent notifications

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Batch release

- Until 2012,the lab tested all biological batches, before being marketed .
- Since 2012 the lab preformed official batch release for plasma products and vaccines (according to OMCL guidelines) .
  - Plasma products – Full monograph according to OMCL
  - Vaccines-According to documents only (Manufacturing protocol, authority release certification)
- Other products-Notification from the QP

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Adverse events using Immunoglobulins- Collaboration between Agencies

- During 2010 it became known of an adverse reaction following the use of an Immunoglobulin from an Israeli Manufacturer (Thromboembolic events) .
- At the same time the same problem was found in an Immunoglobulin from European sources
- After a global regulatory effort it was found that the problem originated from factor XIa residues.
- Three methods were suggested for detecting the impurities .
- As a result the European Pharmacopoeia Monograph was changed
- Test methods were implemented in our laboratory.
- Screening is done pre and post authorization

Plans for the near future

New Technologies – According to the specification of new products coming to the market.

It is important to consider the focus since we are a limited number of analysts.

ATMPs

One of our priority missions is to decide how to release a batch of ATMPs

Batch release-What to add to the documentation, should it be for all the batches or just the first batch?

Is it possible for the laboratory to perform some of the tests on the product?

Limited sample size

Short life time

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THANK YOU