The Republic of Serbia Ministry of Health

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GMP Inspection in Serbia

National regulations in the field of production of medicines

- Medicines and Medical Devices Law ("Official Gazette of the Republic of Serbia" No. 30/10).
- Regulation on conditions for medicines manufacturing ("Official Gazette of the Republic of Serbia, No. 27/08.)
- Guidelines for Good Manufacturing Practice and Annexes 1 - 19 ("Official Gazette of the Republic of Serbia" No. 28/08) comply with directives 2003/94/EC and 91/412 / EEC.
- Guidelines for Good Manufacturing Practice for API ("Official Gazette of the Republic of Serbia" No. 86/10) comply with directives 2003/94/EC and 91/412 / EEC.
- Guidelines of Good Distribution Practice (“Official Gazette of the Republic of Serbia” No. 28/08).

- Medicines and Medical Devices Law, in area of medicines, regulates:
  - The issuance of a license of medicines
  - Medicines pricing
  - Clinical trials
  - Pre-clinical trials under Good Laboratory Practice Guidelines
  - Medicines production
  - Issuing of GMP certificate
  - Medicines distribution
  - Pharmacovigilance
  - Labeling of medicines
  - Advertising medicines
  - Inspections

Regulation on conditions for medicines manufacturing

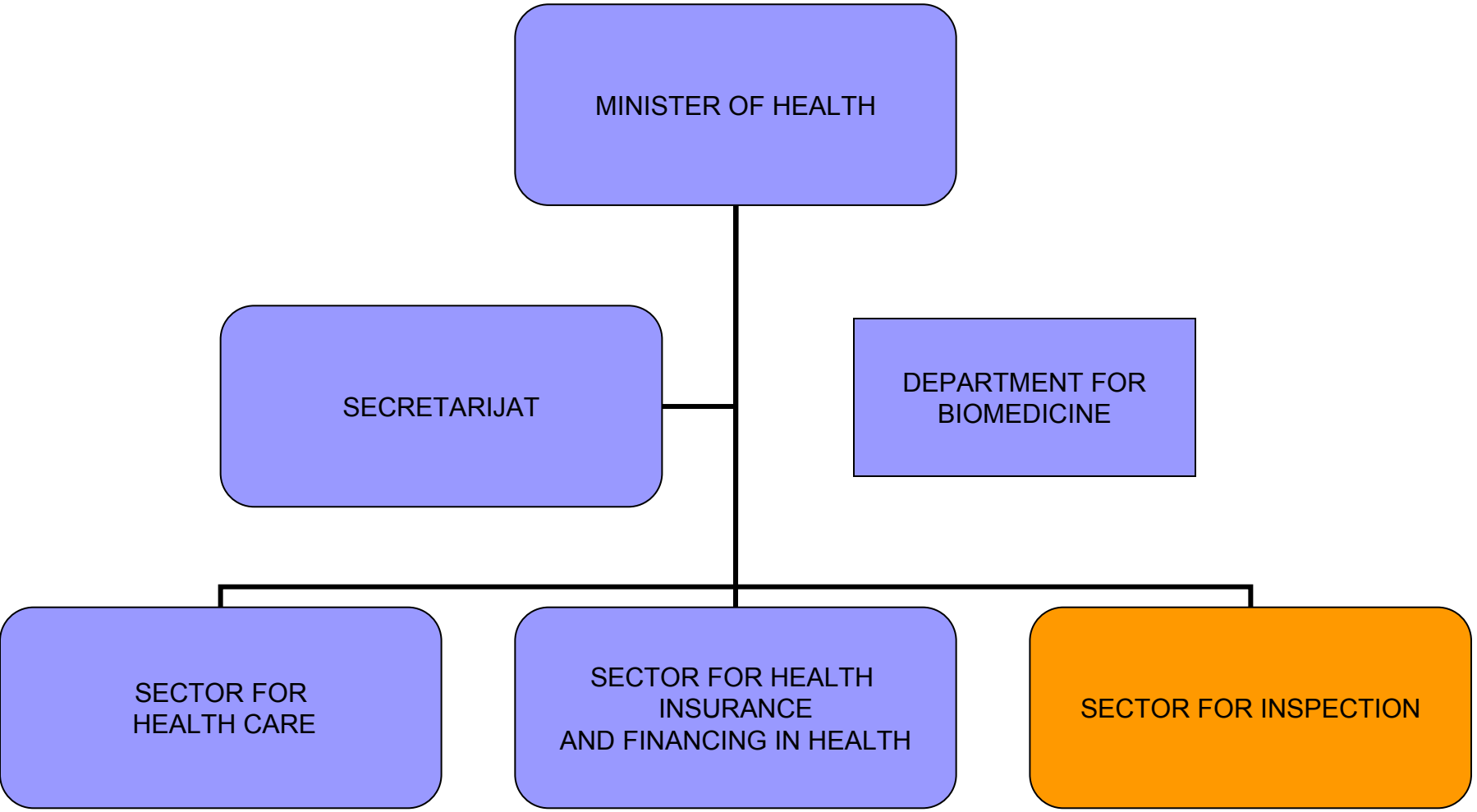
- Regulation on conditions for medicines manufacturing defines the detailed requirements for medicines manufacturing regarded to premises, equipment and staff.

Monitoring of legislation

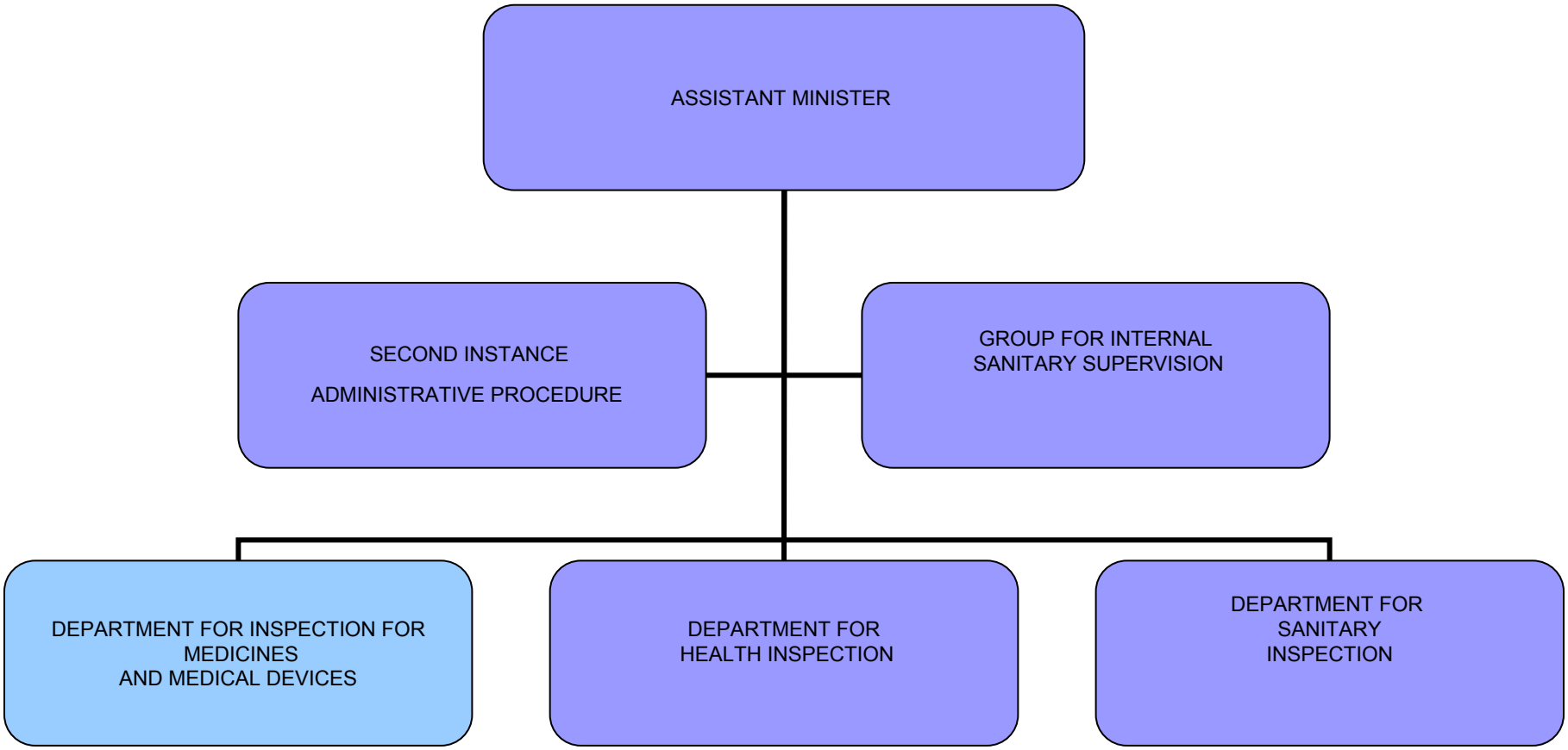
- Inspection of putting this Law and Regulation into effect is perfomed by the Ministry of Health (for Medicines and medical devices for human use), through inspectors for medicines and medical devices, in accordance with Article 208 – 216 of the Law.

- Inspector for medicines and medical devices must have university education (Pharmaceutical or Medical faculty) and at least 3 years relevant work experience.

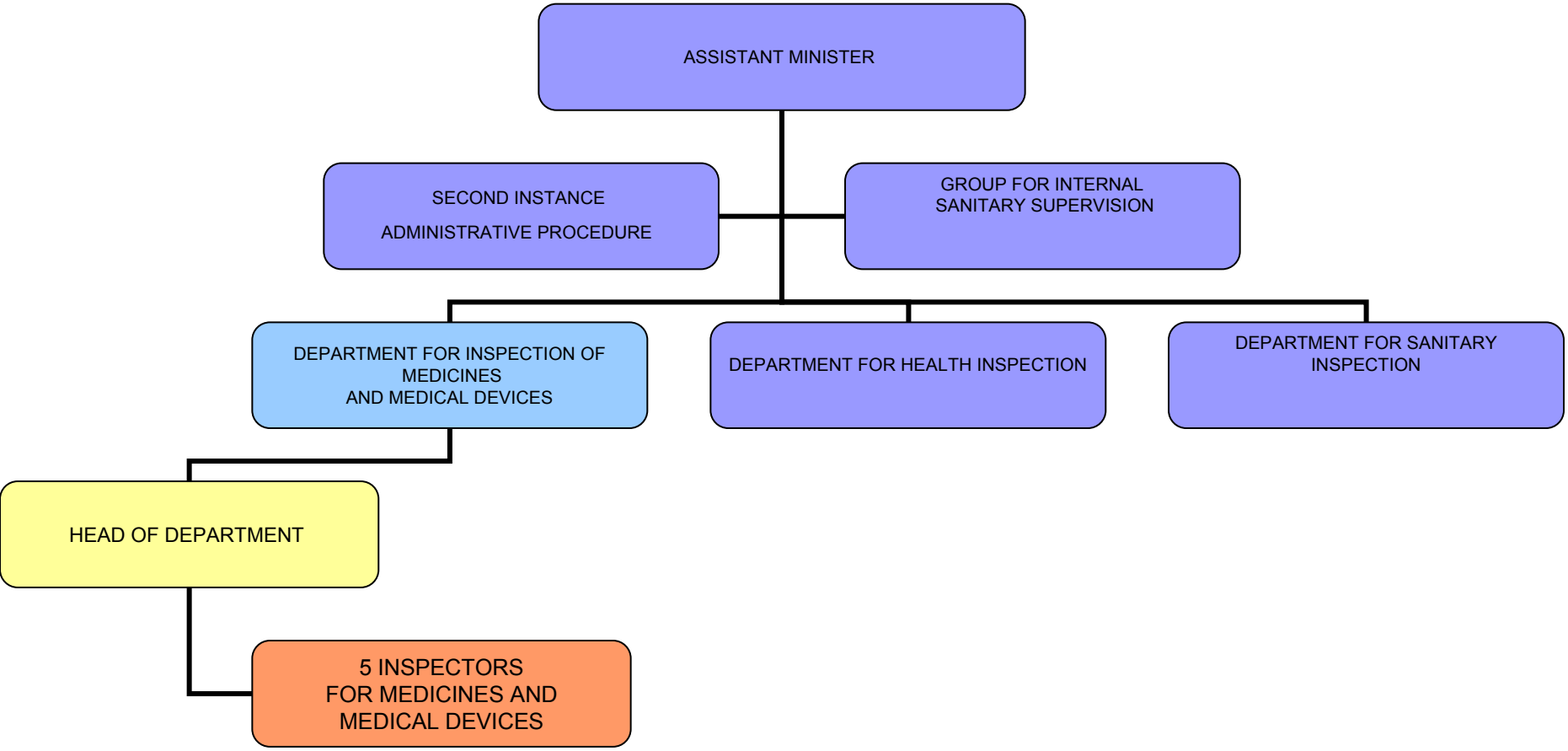
ORGANIZATION CHART MINISTRY OF HEALTH



ORGANIZATION CHART OF SECTOR FOR INSPECTION



ORGANIZATION CHART OF DEPARTMENT FOR INSPECTION OF MEDICINES AND MEDICAL DEVICES



Monitoring the work of inspectors

In accordance with the organization chart of the Ministry of Health

- head of the department monitor and supervise the work of inspectors and
- the work of department is under the control of the Assistant Minister.

Training of inspectors

- Training: In the framework of Twinning project with AFSSAPS, in 2007. and 2008. in Serbia and France conducted the training: GMP, GDP and GPP.
- attending PICs meetings (two times).
- IPA project - attending meetings of working group in EMA.

Procedures

- Department for inspection for medicines and medical devices has 13 SOPs regulating activities of inspectors for medicines, such as:

- SOP 011 - Inspection of medicines manufacturers
  SOP 012 - Issuance of GMP certificates
  SOP 003 - Sampling of medicines
- SOP 001 - Acting upon reports of suspected quality of medicines
- SOP 002 – Recall of medicines from market
- SOP 009 – Decision on suspension of license
  SOP 010 - Training of inspectors of the medicines and medical devices

  which are related to the production and distribution of medicines.

Production of medicines

- The manufacturer is a legal entity that produces the medicines and that can be put into market a series of medicines.
- The manufacturer may have more than one site of production but must have at least one site of batch release.

Medicines production

- Production of medicines involves the entire process of production of medicines or certain parts of the process, the production of API, procurement of start materials, production proces, quality control and batch release, storage and distribution of medicines (art 95 of the Law).

- Production of medicines may perform only legal entity that is licensed to produce medicines issued by the competent ministry.

- Producer of API is not licensed to produce but is obliged to the Ministry of Health reported activity of production of API (art 97 of the Law).

License for manufacturing

- Application for a license for medicines manufacturing have to submit to the Ministry of Health with specific documentation (article 102 of the Law).

- Inspector is in charge:

  - to assess of submitted documentation

  - to perform on site inspection

  - to issue an opinion on whether the conditions for medicines production are fulfilled or not.

Procedure for issuing license for medicines manufacturing

- In accordance with Article 103 of the Law, the Ministry issue a license for medicines manufacturing for:
  - certain manufacturing site
  - certain pharmaceutical form
- The manufacturing license riferes to:
  - the whole production process
  - parts of the production process

The manufacturing license is issued within 90 days of receipt of complete application. The manufacturing license is issued for an indefinite time.

The license includes information about the place of batch release, if the batch release process is performed by manufacturer.

Manufacturing license is signed by the Minister.

Suspension of manufacturing license

- The Ministry may in accordance with Article 107 of the Law revoke a manufacturing license in the case that:

  - the manufacturer does not carry out production in accordance with manufacturing license
  - change the conditions of the license
  - no longer meets the requirements prescribed by the Law
  - do not eliminate the ascertained defects within a specified period
  - the manufacturer submits a request for termination of registration

Manufacturers of medicines

- Currently in Serbia exists 22 manufacturers of medicines with 29 manufacturing sites:
- - 1 manufacturer of vaccines
- - 1 manufacturer of stable blood products (albumin
- and immunoglobulins)
- - 2 manufacturers of medical gases, with 5 sites (medical oxygen, nitrous oxide, medical carbon dioxide)
- - 1 manufacturer of radiopharmaceuticals (radiopharmaceutical kits)

- others:
  - solid dosage forms (sterile and unsterile) - tablets, capsules, powder, freeze-dried forms.
  - semisolid dosage forms (sterile and unsterile) – creams, ointments, suppositories, vaginal suppositories
  - liquid dosage forms (sterile and unsterile) - solutions

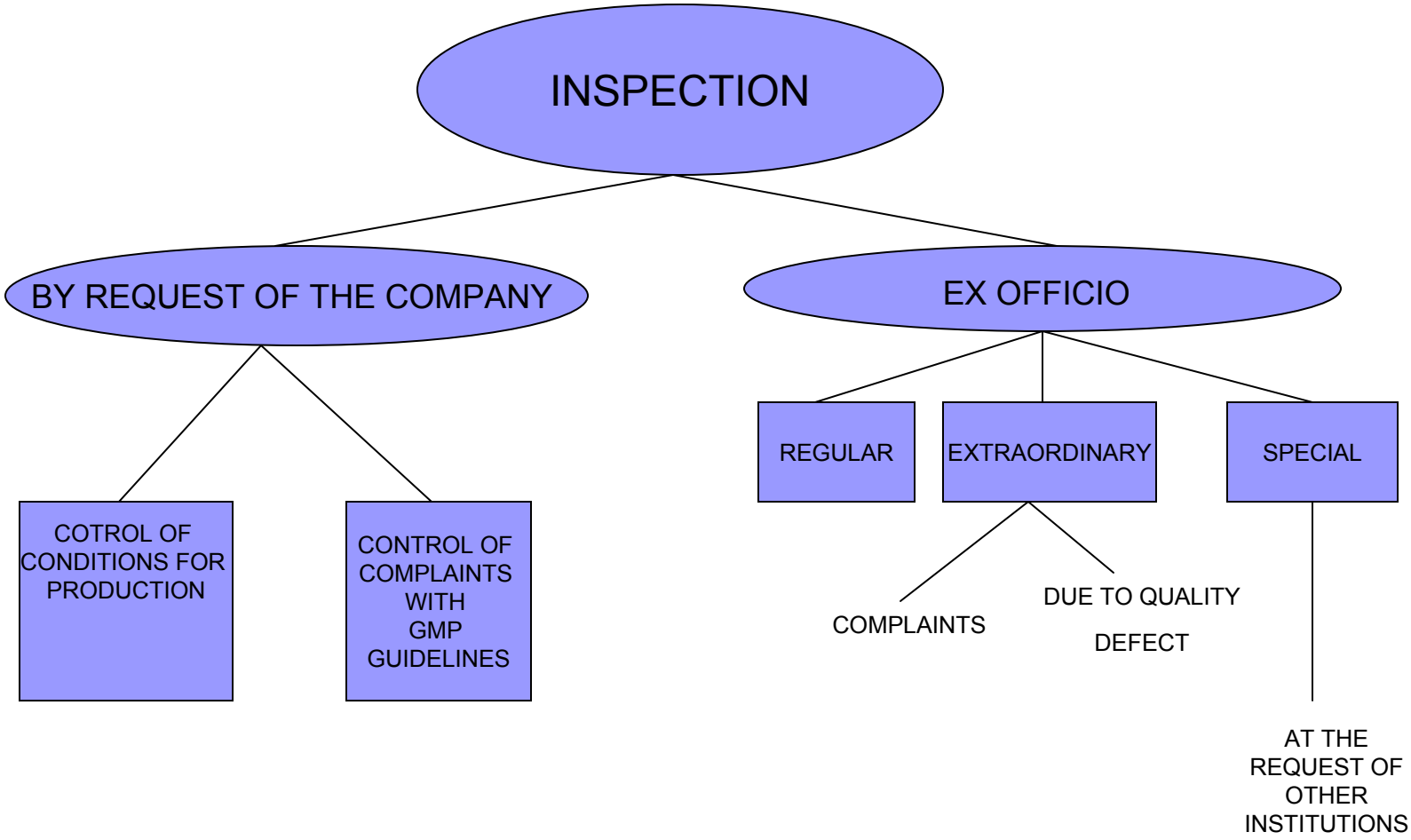
The inspection plan

- Plan for the inspection of manufacturers and checking their compliance with the GMP being prepared at the end of the current year for the next year in accordance with Article 116 of the Law.

- Regular control of manufacturers is provided every 2 years in accordance with the Law.

- According to SOP 011 (Inspection of medicines manufacturers) the control of manufacturer of vaccines and manufacturer of stable blood products is provided every year, and more often if necessary.

Inspections of manufacturer



Inspections of manufacturer

- In 2009. the inspectors conducted 34 inspections of which 8 were in connection with complaints, 6 due to quality defects and 20 others (regular, special,…).

- In 2010. the inspectors conducted 35 inspections of which 4 were in connection with complaints, 5 due to quality defects and 26 others (regular, special,…).

Inspection

- The inspector has the authority to sample medicines in the purpose of checking the quality of medicines in the market. Sampling can be:

  1. regular - in a purpose of quality control of medicines on the market, according to annual plan which is prepared by Agency for Medicines and Medical Devices of Serbia,
  2. extraordinary in case of doubt to quality of medicines.

- Sampled medicines are delivered to the National Control laboratory, Agency for Medicines and Medical Devices.

- Inspectors in the work collaborate with other services such as: Agency for Medicines and Medical Devices, other inspections, police, customs, courts.

GMP certificate

- At the request of the manufacturer Ministry of Health issues the Certificate of compliance with Good Manufacturing Practice, for a period of 3 years, Article 115 and 114 of the Law.
- The certificate is issued for each manufacturing site, quality control and batch release for specific dosage form of medicines.
- According to Article 112 of the Law Inspector for medicines and medical devices (team of 2 inspectors) controls the compliance of manufacturing medicines or active substances with GMP Guidelines.

The Inspection Report

- In accordance with Article 113 of the Law during the inspection the inspector shall prepare a report on compliance with GMP Guidelines that is delivered to manufactrurer within 30 days.
- Regarding to the report a manufacturer can make comments or suggestions to removal deficiencies within 15 days.
- After the evaluation of proposals or objections, inspector makes a final report with a conclusion on compliance with the GMP Guidelines.
- Based on the final report, the Ministry issues a certificate of conformity with GMP Guidelines. Certificate is signed by the Minister.

GMP certificate

- Currently:
  - Since 2006. until now inspectors for medicines performed 64 inspections on the site related to GMP compliance

  for 7 producers of medicines for solid dosage forms, semisolid dosage forms and liquid dosage form (sterile and unsterile)

List of experts

- In accordance with Article 112 of the Law, Minister of Health determines the experts who can participate in the process of conformity of production with the GMP Guidelines.

- Experts from the list of experts for the process of determining compliance can participate in determining the conformation only in the presence of inspectors.

- Formation of the list is in the process.

Compliance with the GMP Guidelines

- Medicines and Medical Devices Law ("Official Gazette of the Republic of Serbia" No. 30/10) gives to manufacturers of medicines, which already have a license to manufacture, a term of 18 months (from 15 may 2010) for compliance with Good Manufacturing Practices (Article 222 of the Law), except for producers who are in the process of privatization or are established as a health care institutions that have 3 years.

Database

- Department maintains the Register of licenses issued for the production of medicines in accordance with Article 104.
- In accordance with Article 97 of the Law department will maintain a register of producers of API.

- Department maintains a database in electronic and hard copy of all manufacturers.
- Database contains:

  -issued licenses

  -report of all conducted inspections

  -noted non-compliances.

THANK YOU FOR YOUR ATTENTION