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Cooperation between HALMED and GMP Inspectorate in supervision of manufacturers: Croatia's experience so far

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CONTENT

- CHANGES IN CROATIAN LEGISLATION - RESPONSIBILITIES AND ROLES OF HALMED AND GMP INSPECTORATE IN MINISTRY OF HEALTH AND CO-OPERATION
- CROATIA'S EXPERIENCE IN SUPERVISION OF MANUFACTURERS
- MANUFACTURERS IN CROATIA – PRESENCY ON EU MARKET AND EU GMP INSPECTIONS
- CONCLUSION

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NATIONAL AUTHORITY

According to national Law in the field of medicinal products for human use there are two national regulatory authorities in Croatia:

- **MINISTRY OF HEALTH (MoH)**

  Ksaver 200A, Zagreb

  www.miz.hr

- **AGENCY FOR MEDICINAL PRODUCTS AND MEDICAL DEVICES (HALMED)**

  Ksaverska cesta 4, Zagreb

  www.halmed.hr

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MINISTRY OF HEALTH

Pharmaceutical Inspection within Ministry of Health supervises GLP, GCP, GMP, GDP, quality control, pharmacovigilance and advertising and information of medicinal products.

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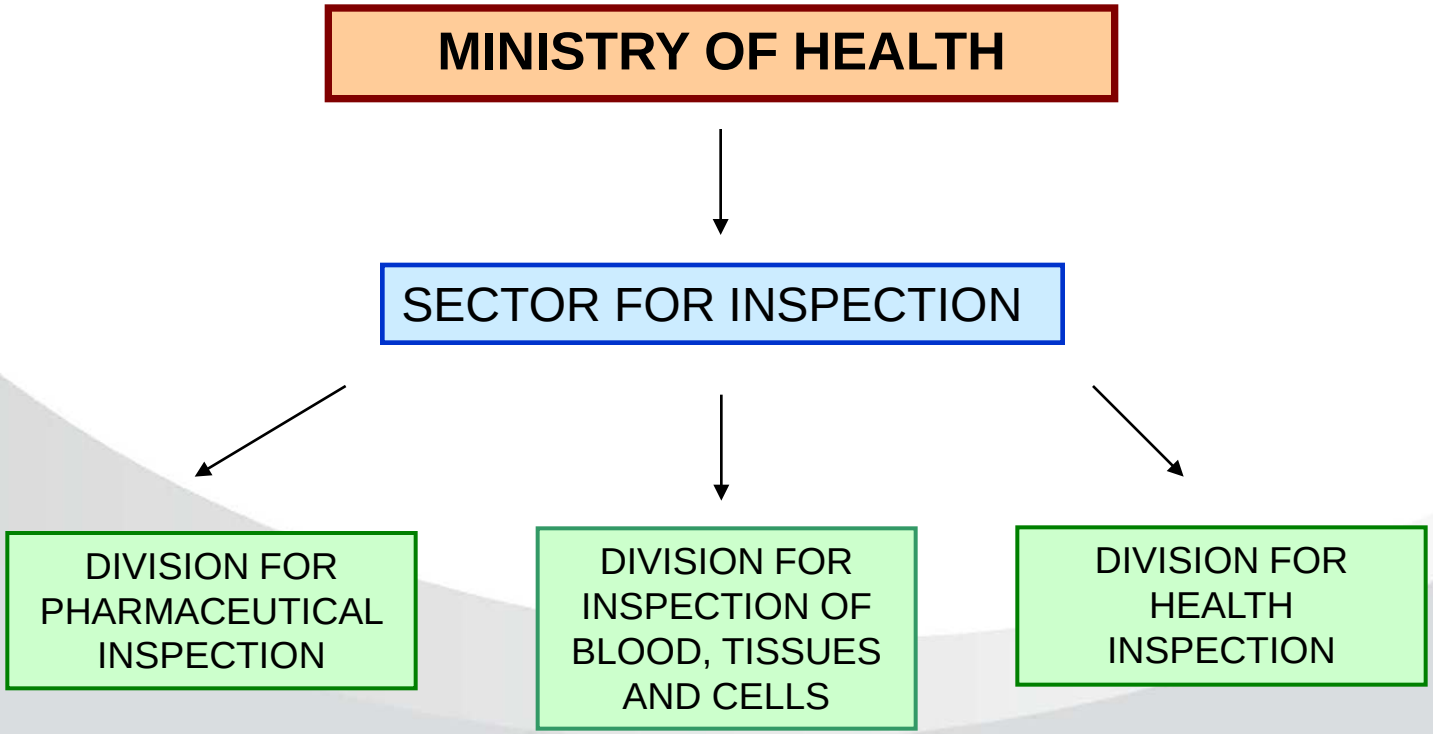
MINISTRY OF HEALTH

ORGANIZATIONAL STRUCTURE



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AGENCY FOR MEDICINAL PRODUCTS AND MEDICAL DEVICES OF CROATIA - HALMED

- Independent institution with public authority
- Medicinal products for human use and medical devices

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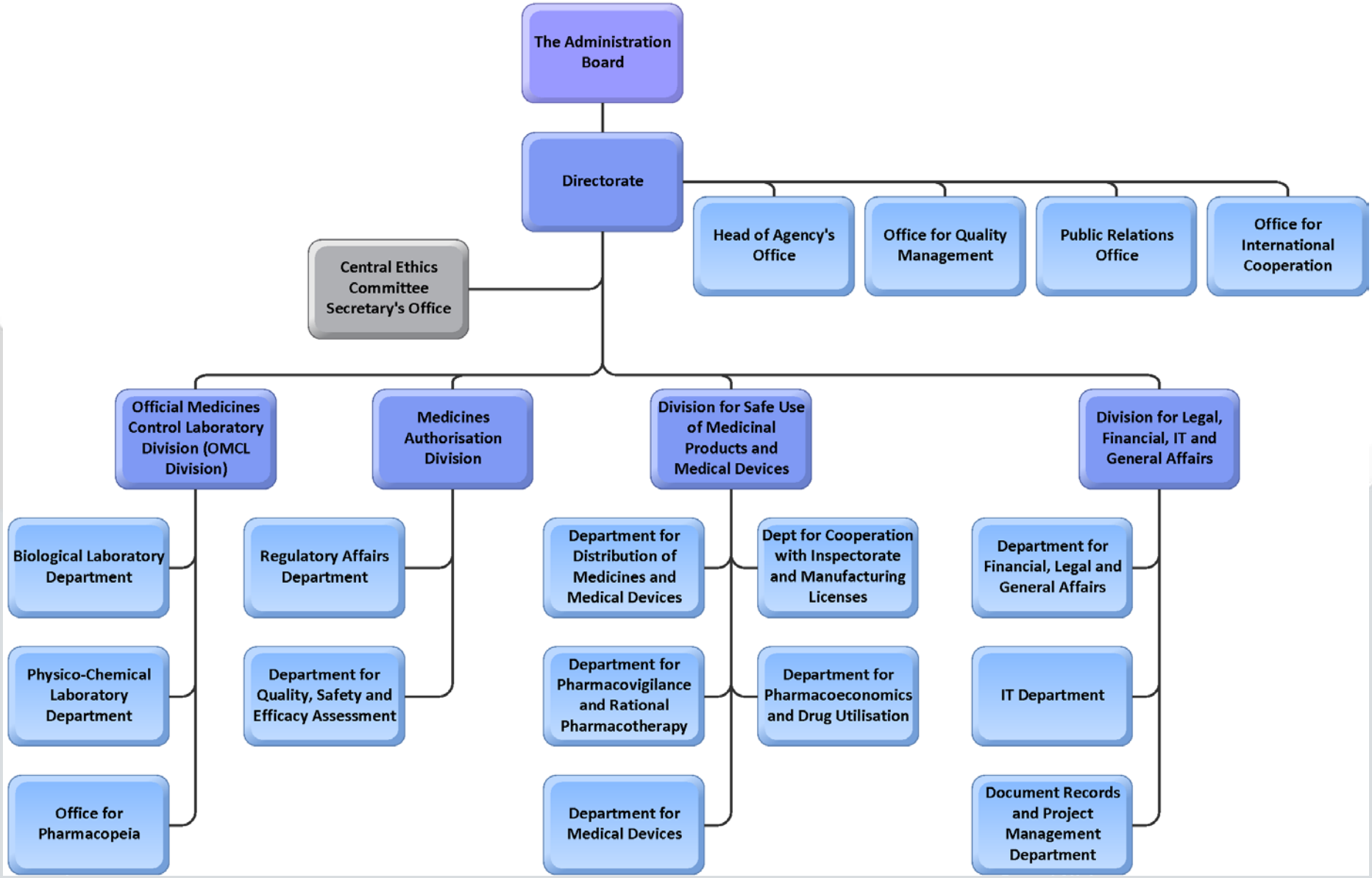

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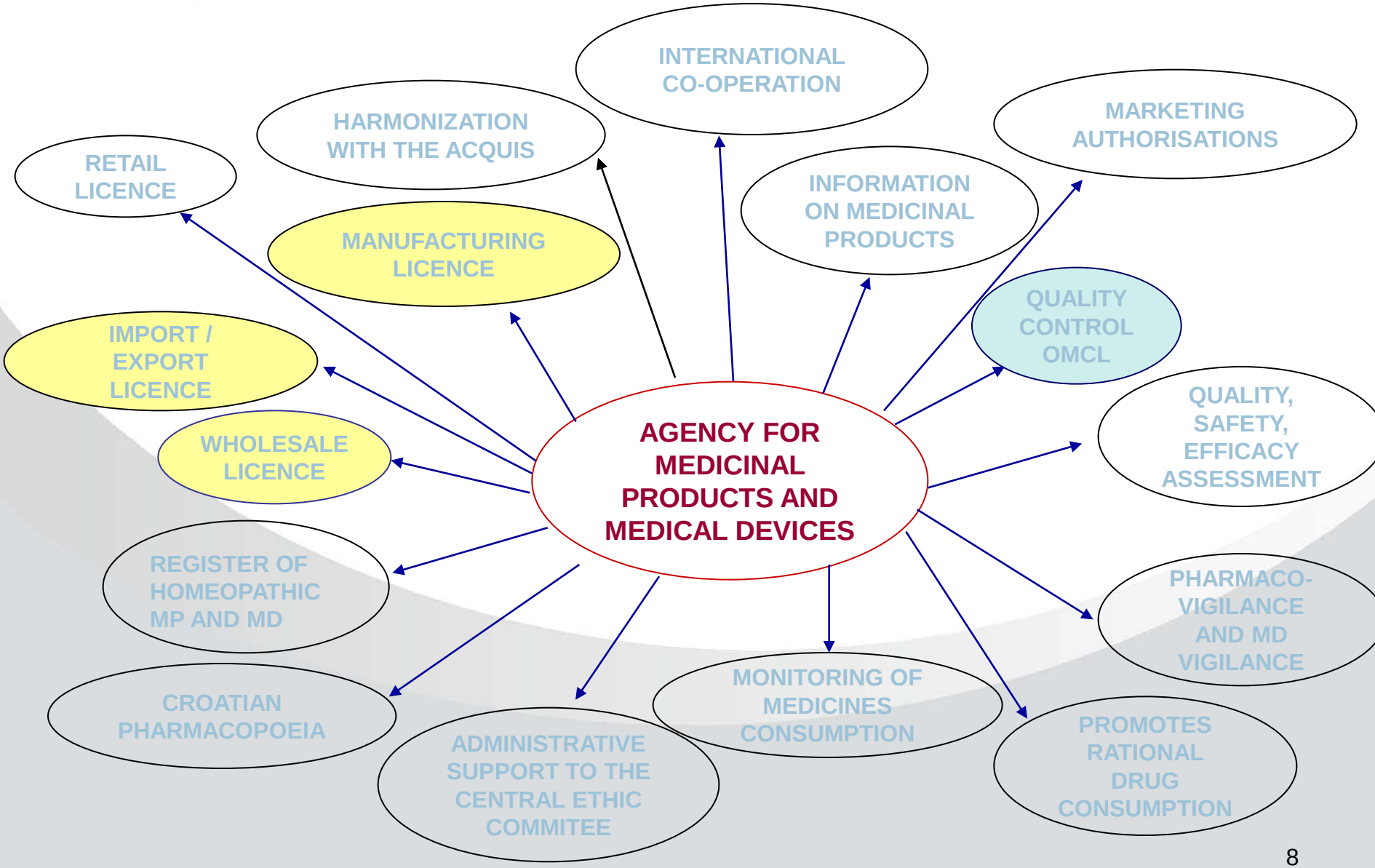
ACTIVITIES OF HALMED



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MANUFACTURE

CROATIA NOW	CROATIA IN EU
Manufacturing authorization obligatory for all manufacturers of finished medicinal products	Manufacturier`s Authorisation (MIA) for manufacturers and importers (of finished medicinal products)
Manufacturing authorization for API manufacturers	Registration of API manufacturers, importers and distributors

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MANUFACTURER` S AUTHORISATION

- **HALMED** issues MIA based on Opinion of pharmaceutical inspector – no change in responsibilities

- Manufacturers application to HALMED
- Audit is done by audit team consisted of pharmaceutical inspector + 1 or 2 experts
- Confirm compliance with GMP, marketing authorisation
- Procedure in 90 days

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MANUFACTURER` S AUTHORISATION changes

CHARACTERISTIC	CROATIA NOW	CROATIA IN EU
VALIDITY PERIOD	5 YEARS OR CONDITIONAL - RENEWAL VARIATIONS	UNLIMITED OR CONDITIONAL VARIATIONS
FORMAT	• SITE ADDRESS • COMPLETE OR PART OF MANUFACTURING PROCESS • PHARMACEUTICAL FORMS • ANNEX - MEDICINAL PRODUCTS LISTED	• SITE ADDRESS • UNION FORMAT FOR MIA • NO ANNEX WITH LIST OF MEDICINAL PRODUCTS

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REGISTRATION OF MANUFACTURER, IMPORTER OR DISTRIBUTOR OF API

- Defined process is similar as for MIA
- Subject to inspection
- Procedure in 60 days

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GMP CERTIFICATE
changes

CHARACTERISTIC	CROATIA NOW	CROATIA IN EU
AUTHORITY	HALMED ON MANUFACTURERS REQUEST	INSPECTORATE WITHIN 90 DAYS OF CARRYING OUT AN INSPECTION
FORMAT	DESCRIPTIVE, FOR PLANT, GROUP OR MEDICINAL PRODUCT	*Union Format for a GMP Certificate*
VALIDITY PERIOD	3 YEARS FROM MIA`S DATE OF ISSUE OR LAST DATE OF GMP INSPECTION COULD BE REDUCED BASED ON INSPECTORS DECISION	COMPLIENCE STATUS IN 3 YEARS SINCE THE DATE OF AN INSPECTION REDUCED OR EXTENDED BASED ON REGULATORY RISK MANAGMENT

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HALMED WEB & EudraGMDP

- On HALMED web is list of all issued manufacturing authorisations and wholesale distribution authorisations – CONTINUE
- EudraGMDP - Public and regulatory available data:

- Manufacturing and import authorisations
- Good Manufacturing Practice (GMP) certificates.
- Statements of non-compliance with GMP
- GMP inspection planning in third countries
- Wholesale Distribution Authorisations
- Good Distribution Certificates (GDP)
- Statements of non-compliance with GDP
- Registration of manufacturers, importers and distributors of active substances for human use located in the EEA

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GMP INSPECTION

ORDINANCE ON CONDITIONS AND PROCEDURES OF ESTABLISHING REQUIREMENTS OF GOOD MANUFACTURING PRACTICE ANDTHE PROCEDURE OF ISSUING MANUFACTURING AUTHORIZATION AND CERTIFICATES OF GOOD MANUFACTURING PRACTICE (Official Gazette 74/09)

- Article 19 recalls EU GMP, Volume 4
- Article 30 recalls Compilation of Community Procedures on Inspections and Exchange of Information

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SUPERVISION OF CROATIAN MANUFACTURERS

Types of Inspections

- Regular inspection every 3 year
- Problem oriented inspection
- At the request of the Agency for issuing manufacturing authorisation

- Experts from HALMED are engaged

- GMP standard is EU GMP

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SUPERVISION OF CROATIAN MANUFACTURERS, 2010-2012

- 16 manufacturers

- 31 audits - inspections
  - 2010 – 11 (8)
  - 2011 – 10 (8)
  - 2012 – 10

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HALMED ACTIVITIES FOR CROATIAN MANUFACTURERS, 2010-2012

	2010	2011	2012
GMP CERTIFICATES	41	50	41
MANUFACTURING AUTHORISATION:			
• **NEW**	2	1	0
• **RENEWAL**	2	2	4
• **VARIATION**	14	15	13
• **WITHDRAWAL (TRANSFER OWNERSHIP OR SUSPENSION)**	2	1	0

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HALMED ACTIVITIES FOR CROATIAN MANUFACTURERS, 2010-2012

OMCL

MARKET SURVEILLANCE

- Pharmaceutical inspector (MoH) approves annual plan (taking into consideration proposal made by Agency) and takes samples from the market
- OMCL performs QC of samples taken by MoH
  - 2010 - 112
  - 2011 - 117
  - 2012 – 77 (analysis of some MP has not been finished yet due to reference standards delay or Analitical report issuing)

QUALITY DEFECTS

- Pharmaceutical inspector (MoH) takes samples, performs GMP or GCP inspection, suspend medicinal product
- OMCL performs QC of samples

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Quality Control

VACCINES

Quality Control (performed by Agency)

REGULAR	SPECIAL	OFF-SHELF	EXTRAORDINARY
Every Batch of MP imported in Croatia	First Batch of every Medicinal Product after MA	Samples taken from the Market by Pharmaceutical Inspection (MoH)	Requested by MoH Or Agency
For EU products Agency accepts certificates from EU	Every Batch of Immunological and Blood Product	At least once in 5 years	In case of Suspicion on Quality
Deadline: For EU products: 8 days For all other: 30 days	Other Medicinal Products (regulated by MoH)		

Deadline: 30 days

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OMCL – Quality control

- From the day of accession to the EU OMCL analysis of first batches and imported batches will be discontinued
- In focus will be market surveillance
- New rules for importers
- MRA agreements

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GMP CERTIFICATES FOR CROATIAN MANUFACTURERS FROM EU NATIONAL AUTHORITIES

MANUFACTURER	SITE ADDRESS	NCA	ARTICLE OF DIRECTIVE/REGULATION	DATE OF INSPECTION D/M/YYYY	SCOPE	NOTE
BELUPO Pharmaceuticals and Cosmetics, Inc.	Ulica Danica 5, 48 000 Koprivnica, Croatia	STATE INSTITUTE FOR DRUG CONTROL	Art.111 (4) _ 2001/83/EC Art. 15 (4) _ 2001/20/EC	28.9.2012	non-sterile, 1°&2° packaging, quality control - microbiological non-sterility, chemical-physical	IMP
FARMAL d.d.	Branitelja domovinskog rata 8, Ludbreg, 42230, Croatia	AGENŢIA NAŢIONALĂ A MEDICAMENTULUI	Art.111 (4) _ 2001/83/EC	14.1.2009	2 ° packaging	expired
GENERA Analitika d.o.o.	Svetonedjeljska 2, Kalinovica, 10436 Rakov Potok, Croatia	JAZMP	Art.111 (4) _ 2001/83/EC	3.6.2011	quality control - microbiological non-sterility and sterility, biological, chemical/physical	
Hospira Zagreb d.d.	Prilaz baruna Filipović 27/D, Zagreb, 10000, Croatia	Main Pharmaceutical Inspector	Art. 19 (3) of R 726/2004/EC	9.9.2011	sterile, small V, biotechnology; biological API, quality control: chemical/physical, biological	
Hospira Zagreb d.d.	Prudnička cesta, Prigorje Brdovečko 10291, Croatia	Main Pharmaceutical Inspector	Art. 8 (2) of R 726/2004/EC	7.9.2011	2 ° packaging	
JGL d.d.	Svilno bb, Čavle, 51219, Croatia	JAZMP	Art.111 (4) _ 2001/83/EC	20.10.2011	sterile: aseptically, non-sterile: tablets, 1°packaging, quality control: chemical/physical	
JGL d.d.	Pulac bb, Rijeka, 51000, Croatia	JAZMP	Art.111 (4) _ 2001/83/EC	20.10.2011	quality control - microbiological non-sterility and sterility	
JGL d.d.	Pulac b.b., 51000 Rijeka, Svilno b.b., 51219 Čavle, -, Croatia	JAZMP	Art.111 (4) _ 2001/83/EC	5.5.2010	non-sterile: semi-solids	
KRKA-FARMA d.o.o.	Cvetković bb, Jastrebarsko, 10450, Croatia	JAZMP	Art.111 (4) _ 2001/83/EC	29.9.2011	non-sterile:tablets, quality control: microbiological non-sterility, chemical/physical	
Messer Croatia Plin d.o.o.	Slavonska 6, Kutina, 44320, Croatia	JAZMP	Art.111 (4) _ 2001/83/EC	7.12.2011	non-sterile (medicinal gases); quality control chemical/physical	
Messer Croatia Plin d.o.o.	Industrijska 1, Zaprešić, 10290, Croatia	JAZMP	Art.111 (4) _ 2001/83/EC	7.12.2011	non-sterile (medicinal gases); quality control chemical/physical	
PLIVA CROATIA LTD	Prilaz baruna Filipovića 25, Zagreb, 10000, Croatia	MHRA	Art. 8 (2) of R 726/2004/EC	5.9.2011	sterile (aseptical and terminally sterilised), non-sterile, strilisation of API, 2 ° packaging, quality control - microbiological non-sterility and sterility, biological, chemical/physical	
PLIVA CROATIA LTD	Prilaz baruna Filipovića 25, Zagreb, 10000, Croatia	Main Pharmaceutical Inspector	Art. 19 (3) of R 726/2004/EC	5.9.2011	2 ° packaging; quality control: sterility, biological	

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GMP CERTIFICATES FOR CROATIAN MANUFACTURERS FROM EU NATIONAL AUTHORITHIES

- Human Medicinal Products
- 7 manufacturers (one no longer present)
- 10 sites
- 12 valid GMP certificates issued by 5 NCA from 5 EU Member States:
  - 3 - Main Pharmaceutical Inspector, POLAND
  - 1 - STATE INSTITUTE FOR DRUG CONTROL, SLOVAKIA
  - 7 – JAZMP, SLOVENIA
  - 1 – MHRA, UK
  - 1 - AGENŢIA NAŢIONALĂ A MEDICAMENTULUI, ROMANIA

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GMP CERTIFICATES FOR CROATIAN MANUFACTURERS FROM EU NATIOANAL AUTHORITHIES

- Type of inspection – Third Country Inspection Program
  - 1 - Art. 15 (4) of Directive 2001/20/EC - includes IMP
  - 2 - Art. 19 (3) of Regulation 726/2004/EC
  - 2 - Art. 8 (2) of Regulation 726/2004/EC
  - 8 - Art.111 (4) of Directve 2001/83/EC

- Medicinal products manufactured for EU market

EU procedures for marketing authorisation: CP, DCP, MRP

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INTERNATIONAL API INSPECTIO PILOT PROGRAMME

- GMP inspection collaboration on 3rd- country

The 9 joint API inspections conducted under the pilot (5 in India, **1 in Croatia**, 1 in Mexico, 1 in Japan and 1 in China) have helped to build up confidence between the participants, and have facilitated better use of EU/FDA combined

- June 2009
- Joint inspection team: Europe (UK on behalf of EMA) / FDA
- Pharmaceutical Inspection of Ministry of Health from Croatia participated

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CONCLUSION

- LEGISLATION IN CROATIA WAS IN BIG RATE EQUIVALENT TO EU AND EU GUIDELINES ARE FOLLOWED
- NEW LEGISLATION IMPLEMENTS AMENDED EU DIRECTIVE
- SUPERVISION OF MANUFACTURERS IS REGULARLY DONE
- CROATIAN MANUFACTURERS ARE ALREADY PRESENT ON EU MARKET

Thank you for your attention!