SITE MASTER FILE

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Good Manufacturing Practice (GMP) for finished Pharmaceuticals (WHO, EEC, PIC)

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Prepared by:	Verified by:	Approved by:
B.S.Pharm. Nikola Kocev _____	B.S.Pharm.Spec.Prim. Romil Sandzakoski _____	B.S.Pharm.Spec. Blagica Jakimovska _____
Quality Management and Environmental Management		

CONTENTS:

C.1. GENERAL INFORMATION

NAME:

"INTER-EVROGENEKS" d.t.p. Novo Selo

ADDRESS:

Goce Delcev no.12 Str.
2434 Novo Selo

Republic of Macedonia

Phone: **+389 2 3215 800**

Fax: **+389 2 3215 801**

e-mail: **varumin@t-home.mk**

web: **www.interevrogeneks.com**
www.varumin.com.mk

C.1.1 Brief information on the firm

Inter-evrogeneks, Pharmaceutical Industry, was established on December 12, 1998, by M-r Ivan Gjorgjiev with head office located in Skopje, Nikola Vapcarov no.20/7 Str.

In 1999, the factory starts with primary production of own patented herbal medical products. The company has technology for primary processing (chopping, sieving, packaging) and extraction of herbal drugs.

We in Inter-evrogeneks are aware of that quality is the background of every business success and key factor of productivity and market competitiveness. Production and control of pharmaceuticals are carried out in compliance with GMP requirements and other international standards, thus assuring the quality and strict compliance with environmental management standards. From October 2006, Inter-evrogeneks owns GMP certificate issued by the Ministry of Health of Republic of Macedonia.

In 2006, reconstruction and modernization of factory was made, improving the capacities with new equipment for production of solid pharmaceutical forms (tablets).

In September 2007, Inter-evrogeneks certified its environmental management system according to requirements of ISO 14 001 standards. The certification of our company was made also by certification company MKS MAKKONTROL from Republic of Macedonia.

In January 2008, Inter-evrogeneks certified its quality management system according to requirements of ISO 9001:2000 standards. The certification of our company was made also by certification company MKS MAKKONTROL from Republic of Macedonia.

In November 2009, Inter-evrogeneks certified its quality management system according to requirements of ISO 9001:2008 standards. The certification of our company was made also by certification company SGS from Zurich, Switzerland.

Inter-evrogeneks's manufacturing program is composed of medicines for human use (in form of solutions and solids for oral use).

The first registrations of the products were categorized as adjuvant medical products, and from 2009, certain products are registered as herbal medicines.

The quality of Inter-evrogeneks's medicines is regularly controlled by the Institute for Public Health of Republic of Macedonia and Faculty of Pharmacy - Skopje, Republic of Macedonia.

C.1.2 Pharmaceutical manufacturing activities as licensed by the Competent Authorities

In accordance with manufacturing activities approved by Ministry of Health of Republic of Macedonia, Inter-Evrogeneks is producing:

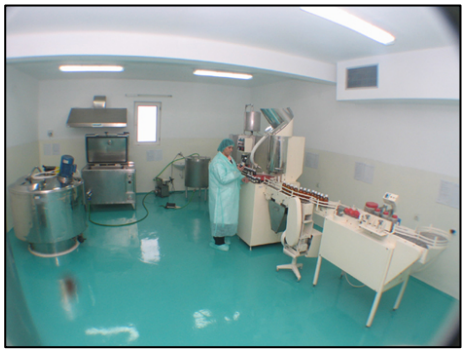
- Finished pharmaceutical products
- OTC products
- Herbal products in different dosage forms

Documents issued by competent authorities:

- Drug marketing authorization (decision) issued by Ministry of Health of Republic of Macedonia. The document is valid for five years, counting from the date of decision's delivery
- GMP and Free sale certificate for products, issued by Ministry of Health of Republic of Macedonia, certifying that the drug is marketed in manufacturer's country and that it is produced according to good manufacturing practice requirements. This document is valid three years from the date of issuing.
- ISO 14001:2004 certificate issued on September 2007, by MKS MAKKONTROL Republic of Macedonia
- ISO 9001:2000 certificate issued on January 2008, by MKS MAKKONTROL Republic of Macedonia
- ISO 9001:2008 certificate issued on November 2009, by SGS Zurich

C.1.3 Any other manufacturing activities carried out on the site.

Storage and transportation, manufacturing and sales, development.

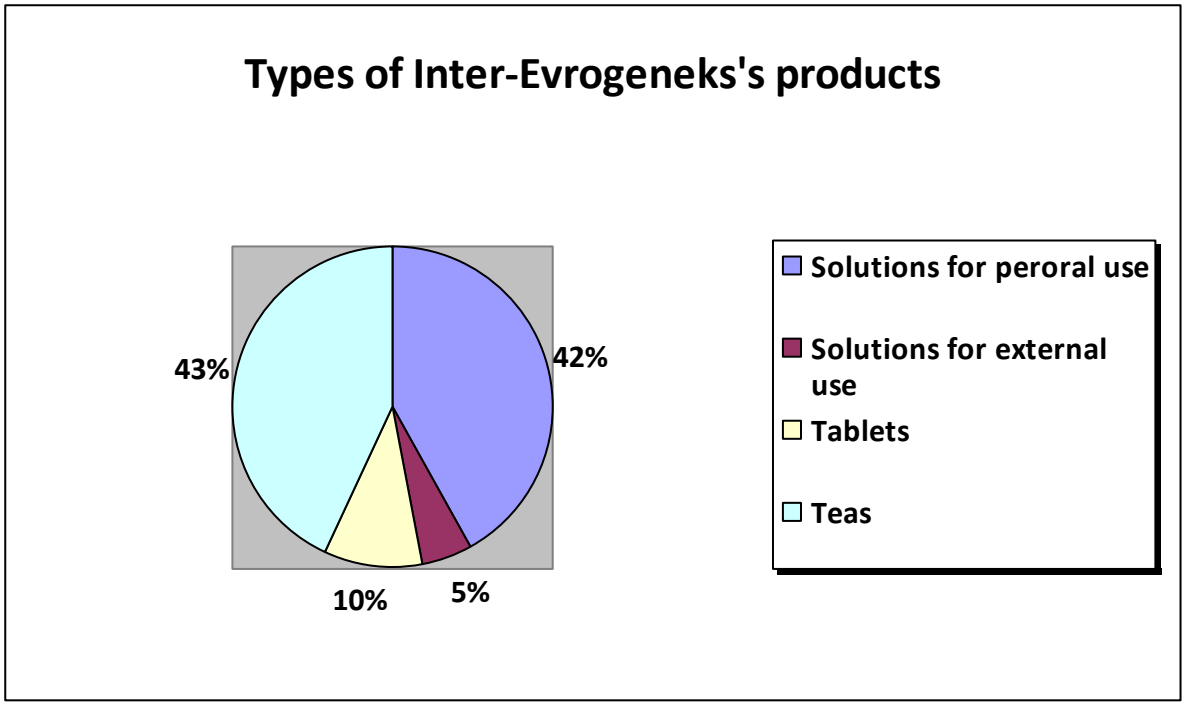


C.1.4 Name and exact address of the site, including telephone, fax and 24 hrs telephone numbers

Inter-Evrogeneks.
Goce Delcev 12, 2434 Novo Selo, Republic of Macedonia
Telephone No. of contact person +389 2 3215 800
Fax No. of contact person +389 2 3215 801
24 hour contact Telephone No. +389 70 214 296

C.1.5 Type of actual products manufactured on the site

Type of Actual Products Manufactured



C.1.6 Short description of the site

INTER-EVROGENEKS, NOVO SELO, REPUBLIC OF MACEDONIA

Inter-Evrogeneks covers the area of 22.000 m^2. The site is located in the Municipality of Novo Selo (located 20 km from the town of Strumica), and it borders with private agriculture land. In is on 4 km from the border of Republic of Bulgaria and 4 km from the border of Republic of Greece.

Surfaces of manufacturing plants are as follows:

- Production plant:	1250 m^2
- Storage area 1:	360 m^2
- Storage area 2:	120 m^2
- Storage area 3:	60 m^2
- Storage area 4:	150 m^2
- Area for preparation of plant material:	120 m^2

Number of employees engaged in the quality assurance, production, quality control, storage and distribution

	TOTAL EMPLOYEES	UNIVERSITY DEGREE
INTER-EVROGENEKS	10	6
Quality Assurance	1	1
Production	4	4
Quality Control	1	1
Storage and distribution	2	/
Technical & Engineering Support Services	2	/

C.1.8 Use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis

- **Institute of Public Health of Republic of Macedonia**
  Address: str. 50 Divizija No.6, 1000 Skopje, Republic of Macedonia
  Tel.: +389 2 3 223 354
  Fax.: +389 2 3 223 033

  With the Institute of Public Health of Republic of Macedonia is made agreement for quality control of each batch and for any other type of analysis.

- **Faculty of Pharmacy Skopje**
  Address: str. 50 Divizija No.6, 1000 Skopje, Republic of Macedonia
  Tel.: +389 2 3 223 354
  Fax.: +389 2 3 223 033

  Inter-Evrogeneks has expert cooperation with the Institute for farmakognosy at the Faculty of Pharmacy Skopje.

- **Faculty of Mathematics and Natural Sciences Skopje**
  Address: Gazi Baba bb, 1000 Skopje, Republic of Macedonia
  Tel.: +389 2 3 249 999
  Fax.: +389 2 3 228 141

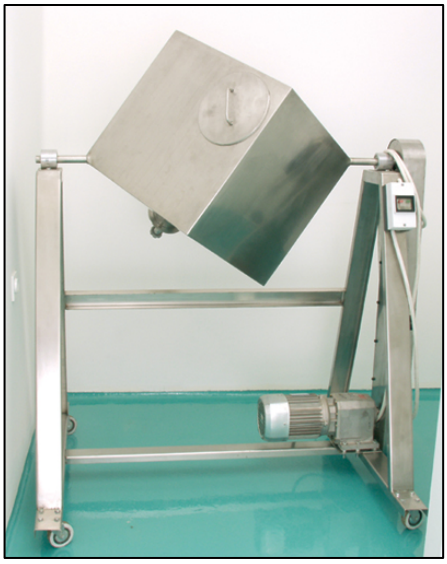
  Part of the comparative analysis and determination of the validated methods are made at the Institute for chemistry at the Faculty of Mathematics and Natural Sciences Skopje.

- **Bulgarian Academy of Sciences**
  Address: str. 15 Noemvri No.1, 1040 Sofia, Republic of Bulgaria
  Tel.: +359 2 979 53 33
  Fax.: +359 2 979 52 23

  Inter-evrogeneks has cooperation with the Department for Microbiology and Virology at the Bulgarian Academy of Sciences.

- **Faculty of Agricultural Sciences and Food**
  Address: blvd. Aleksandar Makedonski bb, 1000 Skopje, Republic of Macedonia
  Tel.: +389 2 3 115 277
  Fax.: +389 2 3 134 310

  Inter-evrogeneks has cooperation with the Department for Microbiology and Parasitology at the Faculty of Agricultural Sciences and Food, Skopje.



C.1.9 Short description of the quality management system of the firm responsible for manufacture

Our quality policy is to meet all the requirements, needs and expectations of our customers and employees. Our goal is to establish and maintain the image of successful and reliable company, to master the new markets and to improve the quality of life with our products.

This is fulfill by strict:
Compliance with GMP guidelines and applying the highest international standards warranting the quality of products and environmental safety; continuous improvement of quality in every business process; permanent training of staff; applying the up-to-date technological solutions; commitment of managers at all levels to continuous quality improvement; involvement of suppliers into our quality system and development of partnerships;

We in Inter-evrogeneks are aware of environmental impact of products and services and we therefore handle our activities according to the Company's Environmental Guidelines. Giving appropriate place to quality and being continuously engaged in Quality policy implementation, we shall meet the needs and expectations of customers.
Company's Management is responsible for implementation of quality policy.

The personnel responsible for Quality Management and Environmental Management has the following responsibilities and authorities:

- development, maintenance and supervision of quality system and environmental management system
- quality documentation management (SOPs, batch production records, batch packaging records, QA Agreements, etc.)
- validations
- supervision of quality system, checks of efficiency and compliance with requirements of quality standards, GMP and ISO standards
- claims processing
- recalls processing
- QA Agreements for contract manufacturing

The quality Management system and environmental system are established, documented, applied and maintained by Inter-evrogeneks and their efficiency is permanently improved in accordance with GMP requirements and ISO 9001:2008 and ISO 14 001 standards.
Efficacy of the system is assured by establishment of work organization and clearly defined authorities and responsibilities as set up in Quality and Environmental Management Manuel, Performance Rules and in individual job descriptions.
The system functioning is supervised through internal inspections / audits (GMP and according to ISO 9001:2008 and ISO 14 001 standards), external inspections and preventive and corrective actions.

Internal audit (ISO 9001:2008 and ISO 14 001) is performed at least once a year and it covers all elements of quality management and environmental management systems. Audit of quality management system can also be done upon customer's requests when willing to meet his requirements, or quality and environmental management systems audits while a contract accomplishment, aimed at system efficacy verification in cases of organizational changes, procedures revision, or in case of doubt in correctness of certain activities performance.
Following the audit, a report is made on performed audit, and conclusions are made on the internal audit. After the audit, appropriate measures are taken to avoid any future mistakes.

Certificate obtained from SGS for quality management according to standards of ISO 9001:2008

SGS

Certificate CH09/2050

The management system of

FARMACEUTSKA INDUSTRIJA INTER-EVROGENEKS

Ul.Goce Delčev 12, 2434 Novo Selo, Macedonia

has been assessed and certified as meeting the requirements of

ISO 9001:2008

For the following activities

Production of medicines and dietetic products

This certificate is valid from 10 November 2009 until 9 November2012
and remains valid subject to satisfactory surveillance audits
Recertification audit due before 27 October2012
Issue 1. Certified since November 2009

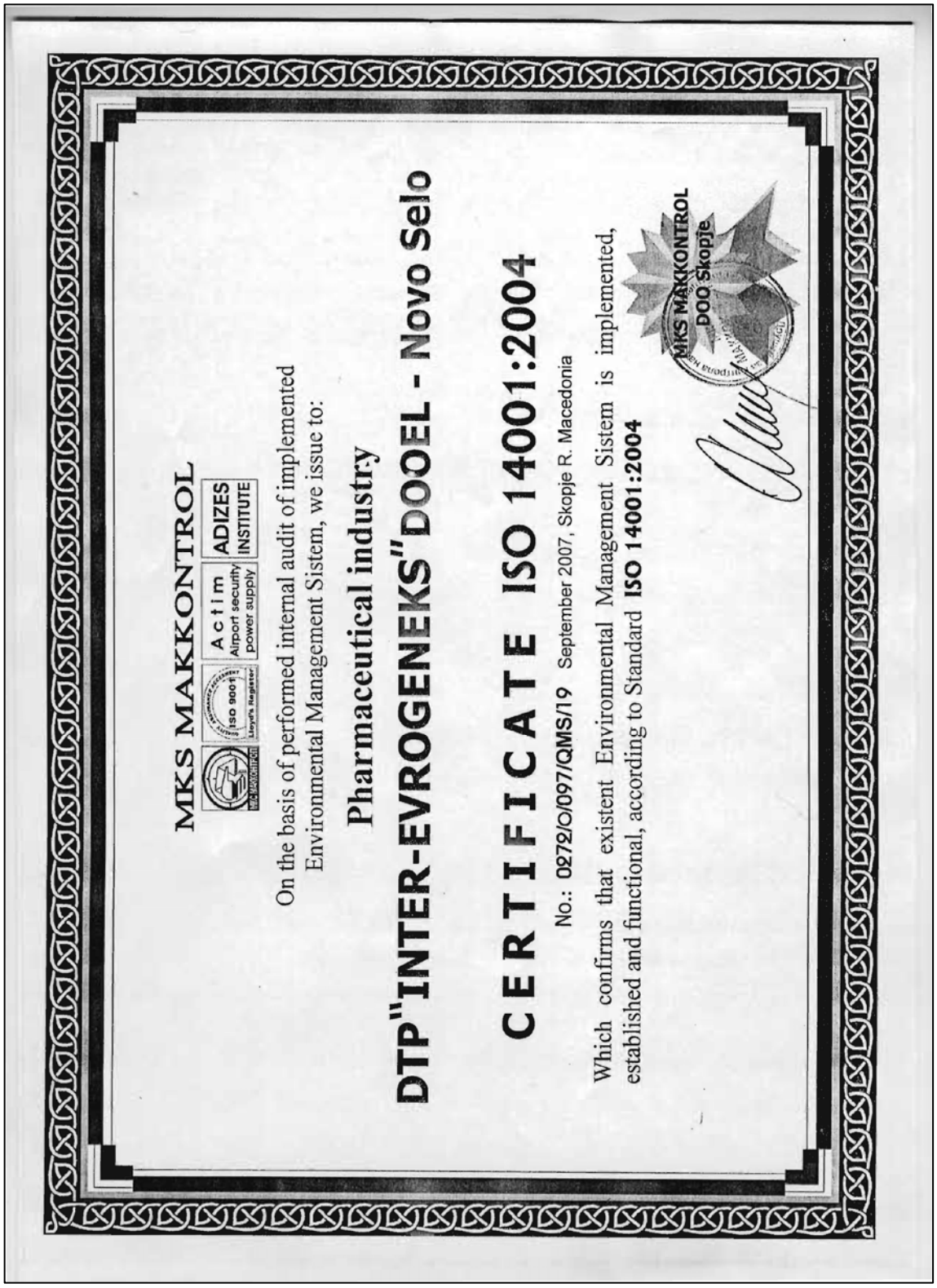
Authorised by

SGS Société Générale de Surveillance SA Systems & Services Certification
Technoparkstrasse 1 8005 Zurich Switzerland
t +41 (0)44 445-16-80 f +41 (0)44 445-16-88 www.sgs.com

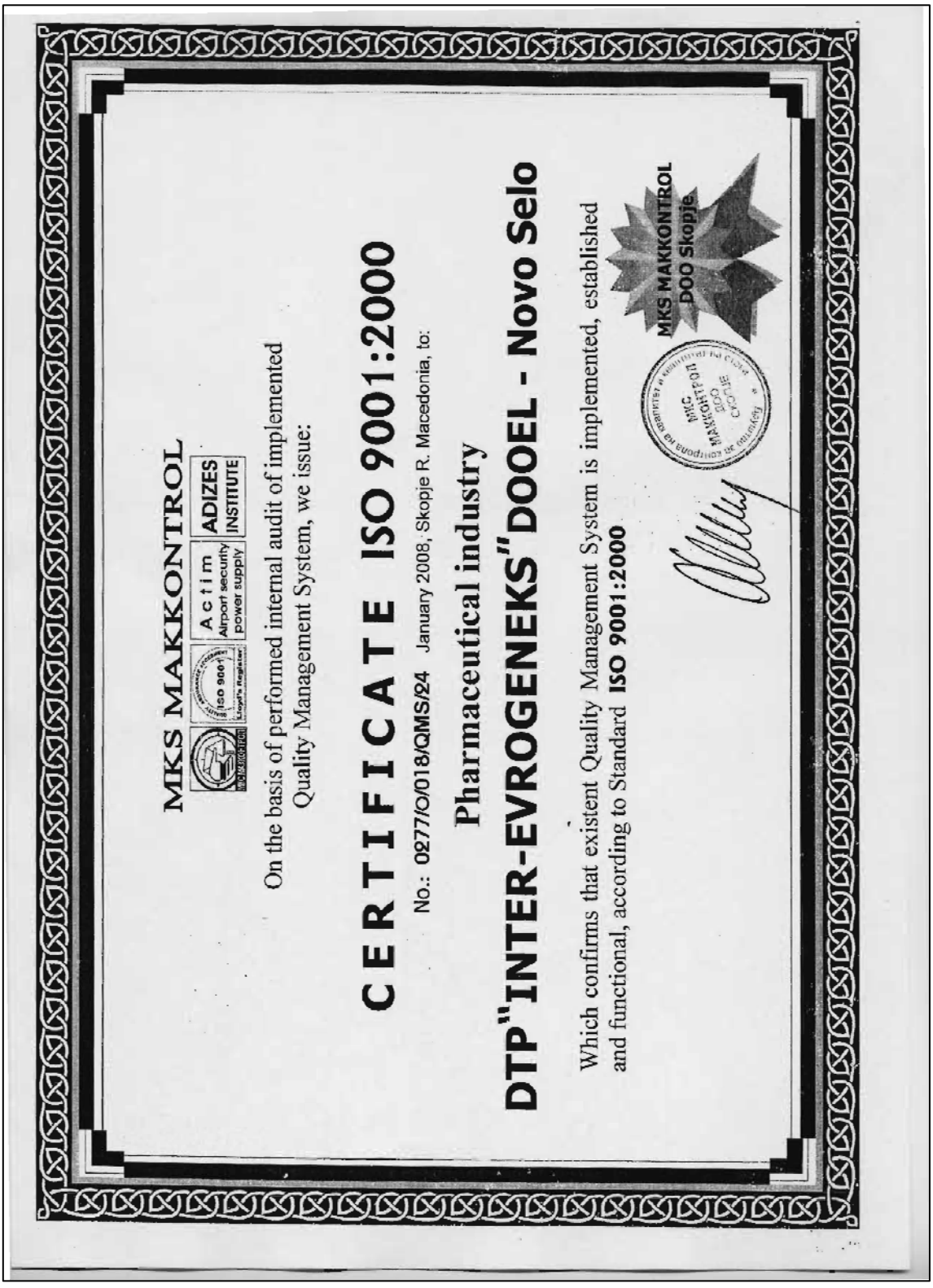
Accreditation No. SCESm 017

Page 1 of 1

Certificate obtained from MKS MAKKONTROL for environmental management according to standards of ISO 14001:2004



Certificate obtained from MKS MAKKONTROL for quality management according to standards of ISO 9001:2000



MKS MAKKONTROL

On the basis of performed internal audit of implemented Quality Management System, we issue:

CERTIFICATE ISO 9001:2000

No.: 0277/O/018/QMS/24 January 2008, Skopje R. Macedonia, to:

Pharmaceutical industry

DTP"INTER-EVROGENEKS"DOOEL - Novo Selo

Which confirms that existent Quality Management System is implemented, established and functional, according to Standard ISO 9001:2000

MKS MAKKONTROL DOO Skopje

Certificate obtained from Ministry of Health of Republic of Macedonia for meeting the requirement of GMP

Republic of Macedonia
MINISTRY OF HEALTH
BUREAU FOR PHARMACEUTICALS

No 15-2082/3
21.04.2010

GMP CERTIFICATE

The Ministry of Health of Republic of Macedonia " 50 Divizija" b.b Skopje, Macedonia, certifies herewith that the manufacturer

Pharmaceutical Industry
„INTER - EVROGENEKS" DOOEL Novo Selo
St. Goce Delcev, No 12,
2434 Novo Selo, Macedonia

complies with the requirements of Good Manufacturing Practice

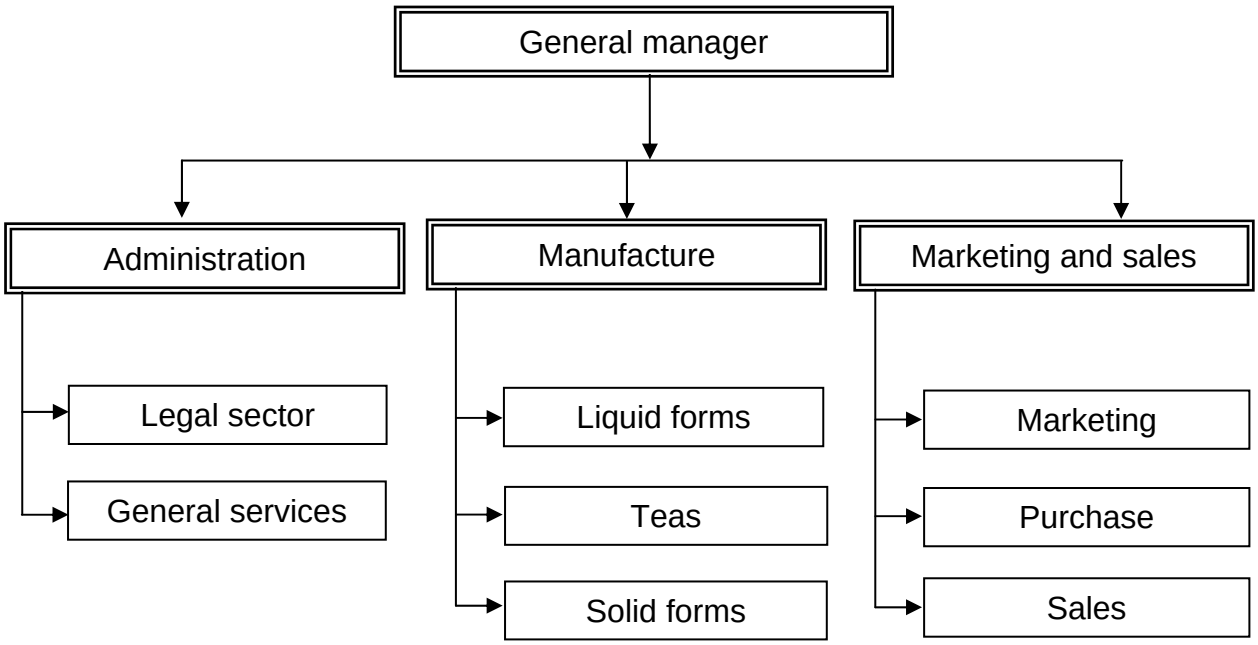
The Ministry of Health certifies that the plants in which herbal products are being manufactured are under constant inspection and the manufacturing meets the requirements of Good Manufacturing Practice in production in accordance with the European Directives and the guidelines of the World Health Organization

Director of Bureau for pharmaceuticals,
M-r Ilco Zaharlev
Signature and Date:

1000 Skopje, "50 Divizija" bb. Tel. N°: +389 2 3112 500: Fax N°: +389 2 3298 435

C.2 PERSONNEL

C.2.1 Organisation chart



C.2.2 Qualifications, experience and responsibilities of key personnel

POSITION	QUALIFICATIONS	WORKING EXPERIENCE (in years)	RESPONSOBILITIES
Ivan Gjorgjiev General Manager	M-r	30	General Manager
Rumjana Gjorgjieva General Secretary	B.S.Tch	25	General Secretary
Blagica Jakimovska Director of production	B.S.Pharm.Spec.	25	Responsible for Pharmaceutical Production
Romil Sandzakoski Advisor	B.S.Pharm.Spec. Prim.	33	Responsible for Pharmacovigilance
Nikola Kocev Quality control	B.S.Pharm.	2	Responsible for Quality Control
Tomislav Angelov Marketing Manager	B.S.E.	22	Responsible for Marketing and sales

C.2.3 Arrangements for Basic and In-service Training and how Records are maintained

Inter-evrogeneks regularly organizes education of the employees through different seminars and training courses and different experiences are constantly exchanged and implemented in the area of production with other companies that have achieved progress in the selected area. The training and the education is conducted by selected person responsible for education, who has qualifications and knowledge of the education area. The education is obligation for each employee and depends from the degree of development of the company in the area of GMP and GLP standards.

C.2.4 Health Requirements for Personnel Engaged in Production

Each employee is obligated, prior to getting employed, to undergo medical check-up determining his/her health capability to perform the assigned job in pharmaceutical industry.
Further on, all employees are obliged to undergo medical check-ups every three years.
Each employee coming in direct contact with product during the job performance is obliged to undergo the sanitary inspection, prior to getting employed. Consequent regular sanitary inspections are carried out according to the plan and program related to current year, and in compliance with Plan and Program of Work Safety in Quality Management and Environmental Management Sector.

C.2.5 Personnel Hygiene Requirements Including Clothing

Personnel working in the manufacturing plant should wear the clean working clothes, trousers, blouses, gloves, caps, masks, clogs, in accordance with procedure. Working clothes and their quality should be appropriate for the work process and working environment to enable product's safety from contamination. Use and changing frequency are proscribed in the procedures. All personnel is well acquainted with hygienic standards required in pharmaceutical production in individual hygienic zones. Every person is expected to come to work clean, tidy and healthy. In manufacturing and laboratory spaces, consumption and keeping of food and drinks as well as smoking are prohibited. Direct contact between operator's hands and starting materials, intermediaries, parts of equipment coming in direct contact with product, is not allowed. All personnel after working must wash their hands in hygienic areas. These areas should be provided with appropriate washing agents (liquid soap and hand disinfectants, paper towels or hand driers).

C.3 PREMISES AND EQUIPMENT

Inter-evrogeneks produces liquid and solid pharmaceutical dosage forms. System of horizontal production line is implemented in the ground floor of the factory, on area of 1250 m^2. All standards are obtained. The used materials meet the requirements of GMP standards, with which the required quality of the product is obtained.
The walls are made from special materials (multi layer laminates) and the finishes are treated with temperature-resistant and chemical-resistant material, which allow quality maintenance of the purity of the area. The finishes of the angles and the edges are made from rubber silicone materials, with which is formed unity of the area. The floors are molded with PVC material with thickness from 10 mm.
The air is treated through HVAC unit where is heated or cooled, humidified or dehumidified, filtered (F4, F6 and F9) and let into the manufacturing areas through absolute filters (EU 13). When passing through the exhaust units, the air is filtered (F9 and EU13) and exhausted in the environment. The number of changes of the air is appropriate for the area of the production. Each HVAC unit is conducted with control of the system and with regular change of the filter. The air of the manufacturing area is removed with extracting AHU systems and is released in the atmosphere, without mixing with the fresh air. Four to eight changes of air are made during one hour, with possibility to increase the number of changes according to the needs. The temperature is maintained on 22°C and the humidity on 55% RH ± 20% RH.

Capacity of system for purified water is 600 lit/h. The system is designed and executed according to GMP requirements enabling the produced purified water quality to meet the requirements of Ph.Eur. The system for purified water is according to requirements of Ph.Eur. and is consisted from:

1. prefiltration
2. softening of the water
3. filtration with active coal
4. adjusting of pH
5. secure filtration
6. UV sterilization
7. electrodeionization (EDI)
8. storage and distribution of the water
9. control system

The water before it is stored in the tank is filtered through filter with size 0.2 µm. The temperature is maintained from 17°C to 19°C. The standards IQ and OQ are implemented. All instruments are calibrated and checked according to the program for assuring the quality of the system.

The technological process is carried out on the following equipment:

- grinding machine for plant material with capacity of 1.000 kg/h
- deionizator for pure water with capacity of 2.000 l/h
- duplexing extractor with capacity of 200 l/h
- homogeniser with capacity of 200 l/h
- dosaging machine for glass bottles with capacity of 10.000 bottles/h
- machine for closing bottles with capacity of 10.000 bottles/h
- labeling machine with capacity of 10.000 bottles/h
- granulator with capacity of 100 l/h
- rotating tableting machine with capacity of 160.000 tablets/h

All machines are constructed according to GMP regulations and all surfaces coming in contact with product are made in stainless steel.

The whole manufacturing process is checked by in-process control, carrying out the analyses and measuring of semi-finished products and finished products. The major equipment for in-process control is composed of:

- pH Meter
- Picnometer
- Balance
- Instrument for determination of hardness of tablets
- Instrument for determination of decomposition of tablets
- Instrument for determination of disintegration of tablets

The responsible personnel for validation is composed of experts in the area of production, quality control, technical personnel and development personnel. For this purpose are made protocols for validation and calibration of the instruments. Also plan-programs for calibration and maintenance of the equipment are made and are kept in separate files.
Inter-evrogeneks has contracts with competent companies for maintenance of the technical systems, equipment and the measuring instruments.
Cleaning procedures for manufacturing areas and equipment are defined in SOPs. Preparing of cleaning material and cleaning techniques are précised within the SOP. Kinds of cleaning agents and their preparation (specific concentration), as well as cleaning frequency are defined in SOPs.

C.4 DOCUMENTATION

Documentation system in Inter-evrogeneks in in compliance with GMP requirements and requirements of ISO 9001:2008 and ISO 14 001 standards and it represents a significant element of quality management and environmental management.

	DOCUMENTS	USED BY
1	Quality policy / Company's Environmental Guidelines	All
2	Quality and Environmental Management Manuel	All
3	Quality and Environmental plans, laws, guidelines, guides	All
4	SOP-quality and environmental system	All
5	Technological, registration, manufacturing, control documentation, operational and examinational instructions, etc.	All
6	Records	All

In Inter-evrogeneks there is an established and documented system of documentation control, covering systemic, process and external documentation.

Internal and external documentation is recorded in the Master Documentation List with the employee in charge of documentation.
All activities related to issuing, approving, revising and filling of documentation and data are defined in documented procedure and instructions.

Documents are stored in various places, depending on nature of document.

Revision on controlled documents are subject to the same requirements of preparing, checking, issuing and approving as the original document and they involve the personnel responsible for original document.
Non-valid documentation in immediately withdrawn from use.

Inter-evrogeneks applies the documentation system through which the status of controlling and testing the materials and equipment in every phase is defined, from receipt, control and testing during the process, through final control up to the final verification and delivery.

Entering control and validated test methods are applied for checking of raw materials quality and packing materials for compliance with specification.

During the manufacturing process and packaging, the compliance with master formula and instructions on manufacturing and packaging are checked.

Preceding the verification and delivery are finished products control and checking of finished products quality compliance with specification.

All checks on compliance with specifications for raw materials, packing materials, intermediate products and finished products are recorded in appropriate forms and as records on quality, verified and approved by competent persons, are filed in the places and for the period as defined in procedures on quality records management.

Receipt control, in-process control and final control are made by employees responsible for quality control. Records on these activities are filed by employees responsible for quality control.

Applying of the established documentation system enables that only the material or product which passed all required controls and which is brought in compliance with all specified quality requirements gets approved for any further processing or use.

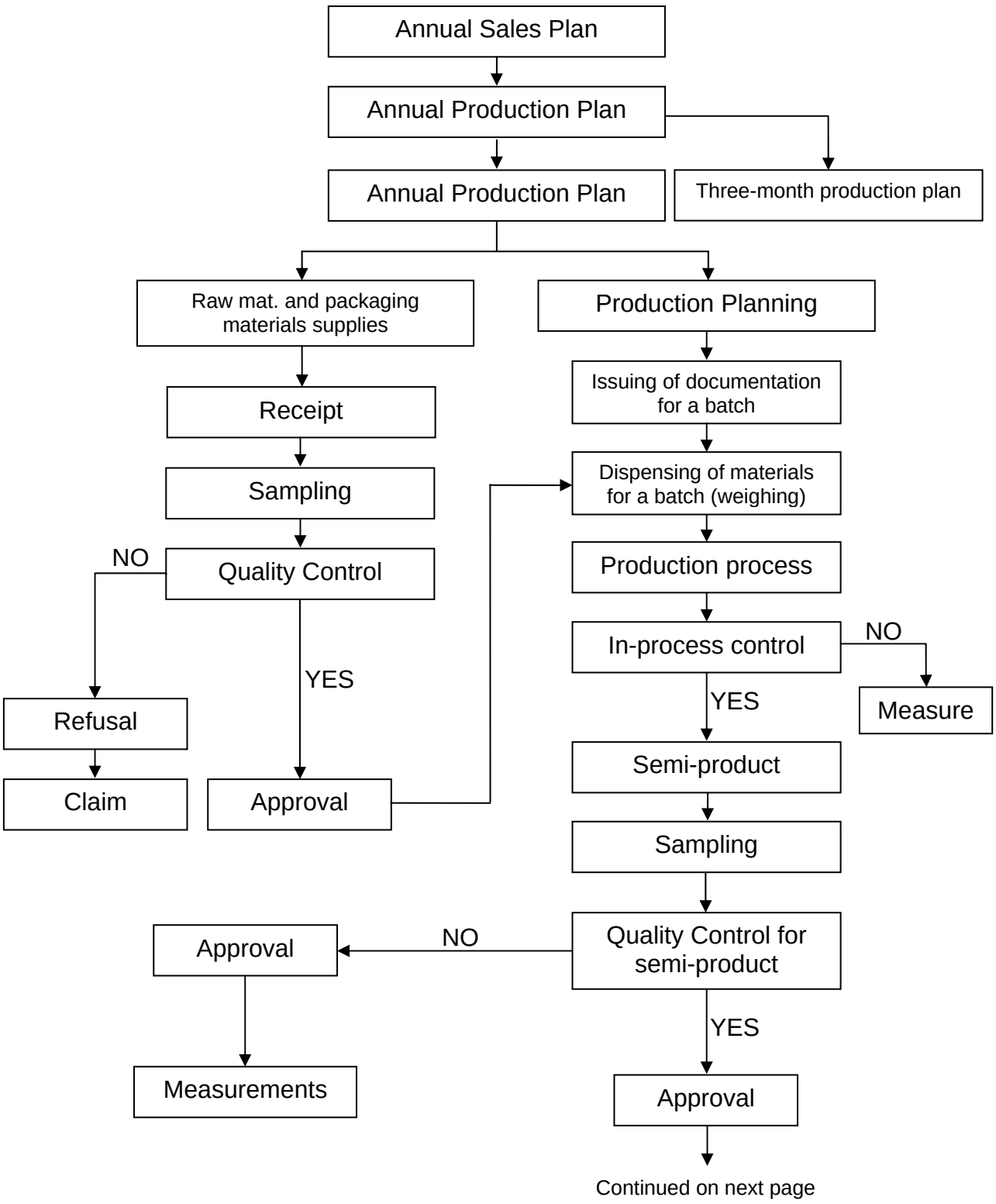
C.5 PRODUCTION

Production in performed in compliance with approved technological procedure. Detailed description of manufacturing procedure together with critical points of process are given in master formula. Production is carried out and headed by competent personnel. During production, the batch production and batch packaging records are filled in. Individual phases, including key parameters, are controlled and documented by in-process control. Separate appropriate procedures are followed for handling of the raw materials, packaging materials, bulk materials and finished products, from taking samples, releasing from quarantine and their final storage.

The process goes under following controls:

- time of mixing (homogenizing)
- temperature of drying
- angle of repose
- reposed and tapped density
- compressibility index
- humidity
- homogeneity of content
- homogeneity of mass
- average mass
- hardness
- fragility
- disintegration

ACTIVITIES CHART



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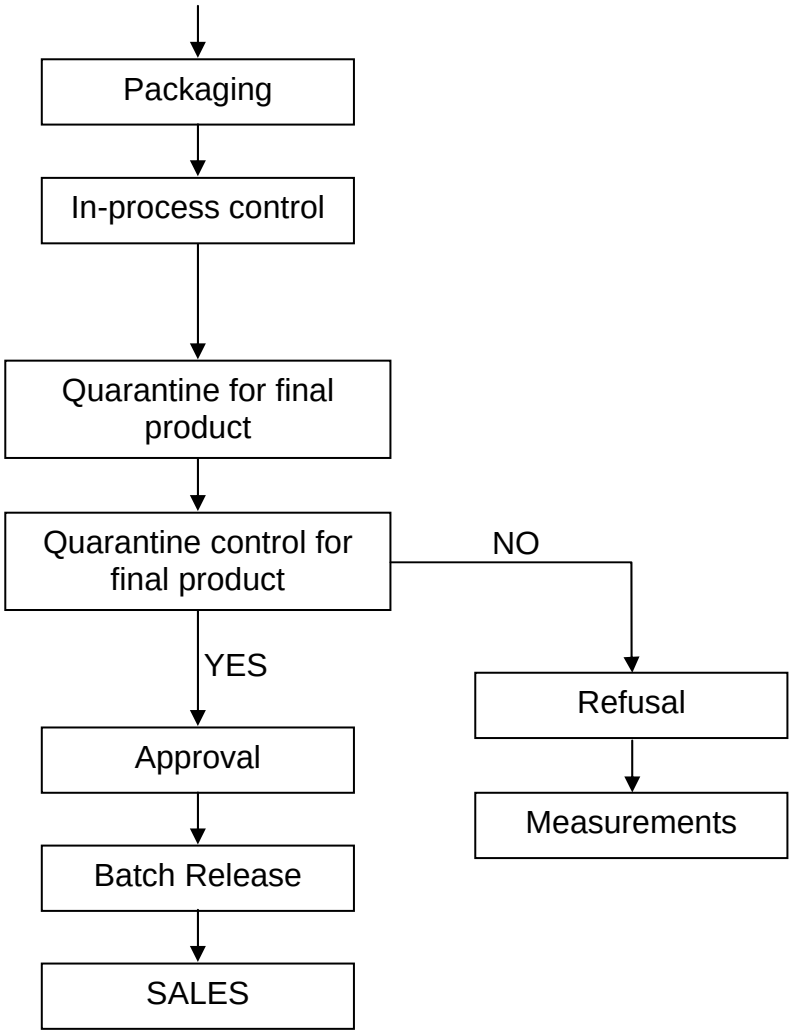
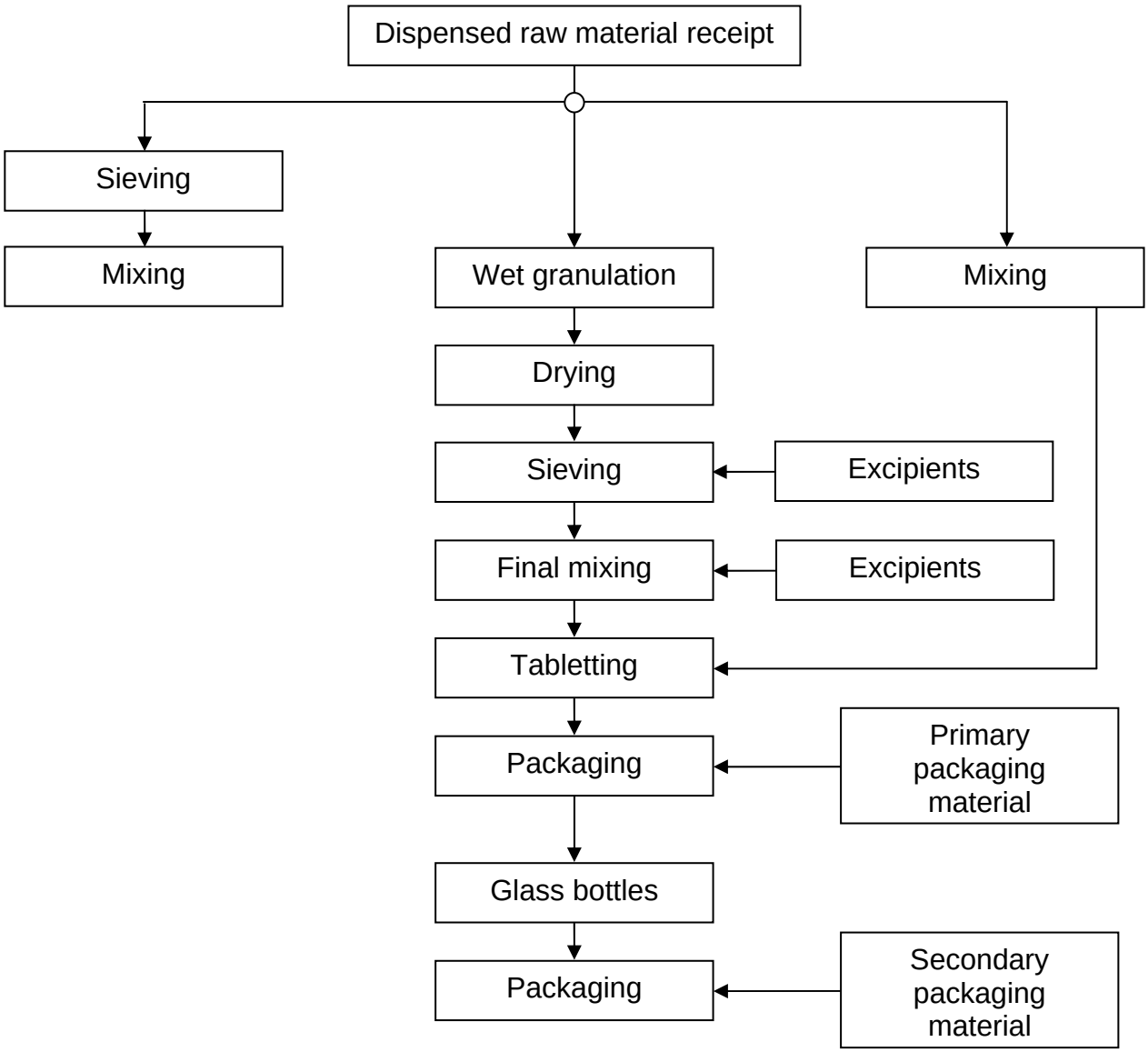
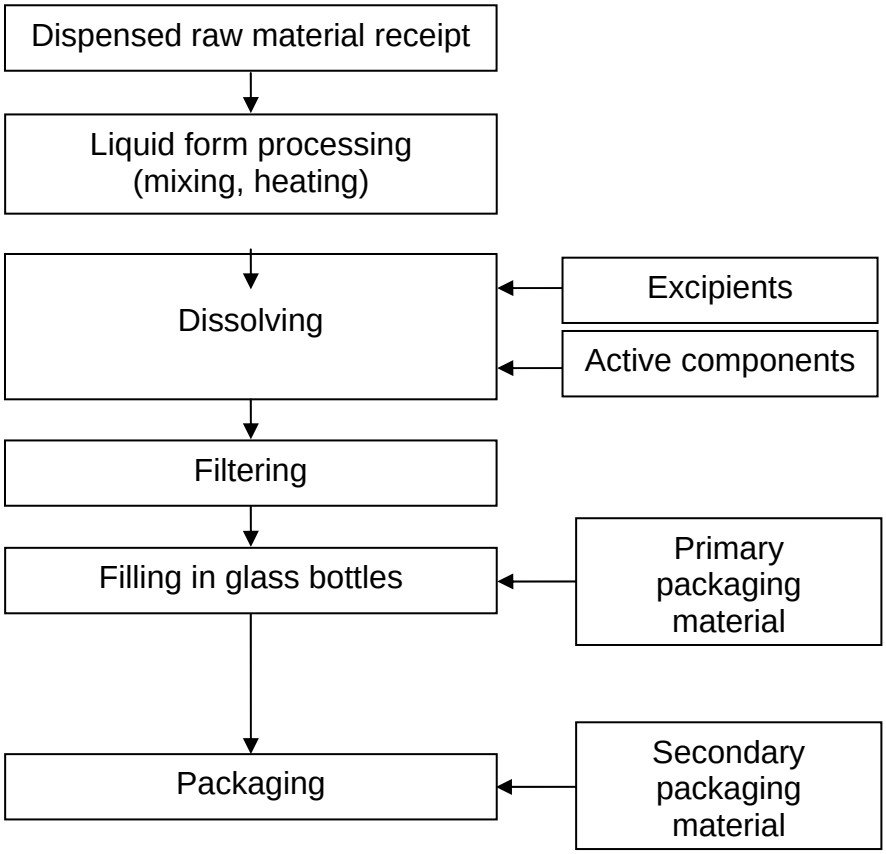


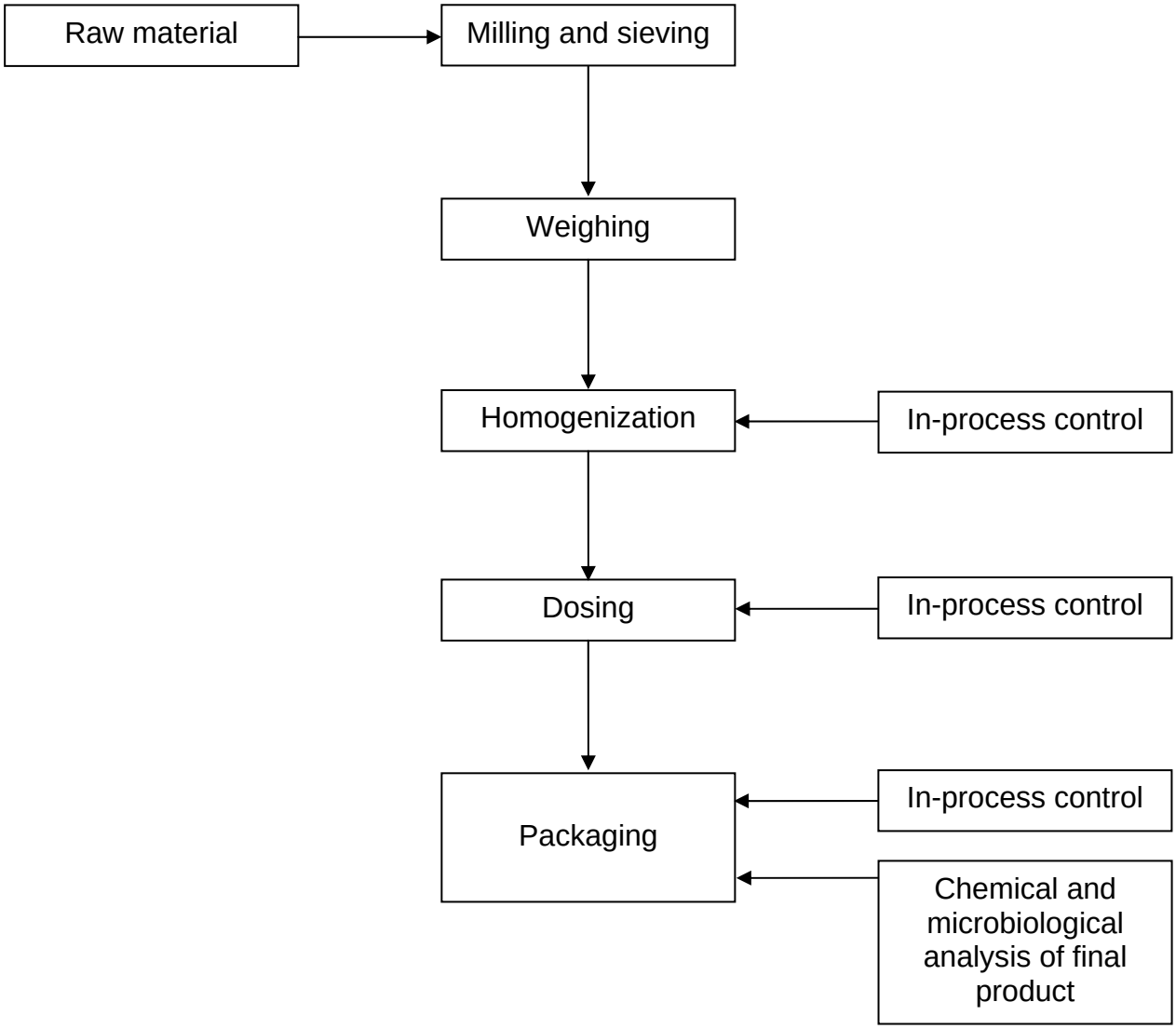
COURSE OF PRODUCTION FOR SOLID ORAL DRUG FORMS



COURSE OF PRODUCTION FOR NON-STERILE LIQUID FORMS



COURSE OF PRODUCTION FOR TEAS



C.5.2. Arrangements for the handling of starting materials, packaging materials, bulk and finished products, including sampling, quarantine, release and storage

Receipt, storage and approving of raw materials

Receipt, storage and approving of raw materials are carried out in accordance with Good Storing Practice (GSP) and Good Manufacturing Practice (GMP) and in accordance with SOPs.
Receipt of raw materials is carried out by competent personnel in compliance with written procedures in Raw Materials Warehouse. The procedure's requirements are as follows:

- checking of compliance for shipment, delivery note (for domestic supplies), invoice (for international supplies), certificate and purchase order; these checks are carried out in area intended for receipt
- labeling of raw materials and moving into the quarantine area
- request for analysis to the appropriate personnel

Sampling is performed following the written instruction in the SOP.

Report on raw materials quality (approval or refusal to use the raw materials) after analysis of samples made in accordance with specifications is issued.

Approved materials are labeled and transferred to intermediate storage within raw materials warehouse. Storing conditions for raw materials are as follows:
- temperature: 10 - 25 °C
- humidity: 50 ± 20 %,

if not otherwise declared by manufacturer / supplier. Temperature and humidity monitoring is made on everyday basis.

Shelves and pallets in intermediate storage are uniformly designated and identified. Only one raw material is allowed to be placed on one shelf / pallet, and at different levels of the same shelf different batches of the same raw material may be placed. The shelves are raised above the floor (height of pallet) and pulled away from walls (15 cm - 25 cm) for easier cleaning of the areas.

Raw materials can be handed out on material requisition slip only and it refers to one batch of raw materials only.

Handing out of materials is done on *first in - first out principle*. Activities of accessories preparing and dispensing are carried out in separate area of hygiene class 3 in raw materials warehouse. Dispensing is done under supervision of production technologist. Non-approved raw materials after the claim settlement are either returned to manufacturer / supplier or transferred according to the procedure to waste material storage.

Receipt, storage and approval of packaging material

Receipt, storage and approval of packaging material are carried out in accordance with GSP principles.
Receipt of packaging material is carried out by competent personnel in accordance with written procedures in packaging material warehouse. The procedures are as follows:

- checking of the shipment compliance with order (name and kind of material, number of purchase order, quantity, manufacturer's certificate…)
- labeling of packaging material and moving into the quarantine area
- request for analysis to the appropriate personnel

Sampling is performed following the written instructions in the SOP.
Report on raw materials quality (approval or refusal to use the packaging materials) after analysis of samples made in accordance with specifications is issued.

Approved packaging materials are labeled and transferred to intermediate storage within packaging materials warehouse. Storing conditions for packaging materials are as follows:

- temperature: 10 - 25 °C
- humidity: 50 ± 20 %,

if not otherwise declared by manufacturer / supplier. Temperature and humidity monitoring is made on everyday basis.

Shelves and pallets in intermediate storage are uniformly designated and identified. Different kinds of packaging material are in separated areas as well as different batches of the same packaging material.
Handing out of materials is done on *first in - first out principle*.
The shelves are raised above the floor (height of pallet) and pulled away from walls (15 cm - 25 cm) for easier cleaning of the areas.
Packaging material can be handed out on material requisition slip only and it refers to one batch of product only.
Non-approved packaging materials are labeled and immediately transferred into not-in-use storage (separated area in packaging materials storage for goods inappropriate for manufacturing process).

Sampling of semi-finished and finished products

Sampling of intermediaries, semi-finished products and finished products is carried out by the appropriate personnel. Sampling is carried out in accordance with written procedures. Every product is sampled according to appropriate sampling plan.

Release of finished products

Release or rejection of a batch of finished product is within the scope of responsibility of Quality Control. System of approving the entering materials and finished product is in accordance with law, current specifications, GMP requirements and international standards.
For production and sales respectively only the entering materials and finished products released by person responsible for release of materials and products can be used.
Decision on release or rejection of a batch of entering material or finished product is based on evaluation of all available information about the batch, like test results, certificates, batch production records, batch packaging records and reports on deviations.
Assessment of information when decision taking on release of finished product for usage is based on reviewing the following documents:

- Batch production records and batch packaging records (weather the information is correctly filled in and is it in compliance with requirements; has the complete description of manufacturing process been given)
- In-process control results
- Results in Report on semi-finished products quality
- Results on environmental conditions monitoring
- Results in Report on finished products quality
- Attestation of in-process control of packed finished product

Report on quality and license for entering material and finished product usage are forwarded to those applying and to those who will use the entering materials and finished products, all according to written procedure. Documentation on batch of incoming material is also recorded, for raw materials - in the period of 10 years, and for packaging material - 2 years. Documentation on finished product's batch is stored one year after expiry of shelf life of the product.

Handling with rejected materials and products

Pharmaceutical waste in Inter-evrogeneks is classified in the following categories:

- Raw materials for production of drugs being damaged at entering the raw materials storage, raw materials with expired shelf life or raw materials intended for products which are not manufactured any more
- Pharmaceutical waste from damaged / inappropriate product during production or development, exhaust from machines, waste from air-conditioning units
- Finished product of expired shelf life
- Filters for dust contaminated by raw materials or by products
- Remainders of tested samples
- Control samples with no longer obligation of retaining (pharmaceutical products) - solid forms
- Product recalls

Every production unit has a container for special waste collection. Every container is marked by label *SPECIAL WASTE*. In the container there is a PVC bag for collecting pharmaceutical waste. Bags containing pharmaceutical waste are to be properly closed and labeled. The label contains data about kind of material, weight and date and signature of responsible person.

Access to storage is allowed to authorized persons only.

Process validation - general characteristics

Process validation protocol contains minimum the following information:

- Purpose of validation;
- Description of production process (chart of process course);
- Major formula;
- List of equipment in use;
- Details about active component(s);
- Test program
    - analysis of critical phases of production process
    - critical process parameters
    - kind of test
    - sampling plan (where, when and how many samples)
    - acceptable limits
- Request for revalidation;
- Persons responsible for performance of validation.

C.6. QUALITY CONTROL

Quality Control is a part of GMP and GLP handling sampling, specifications and testing, as well as organizing, documenting and approving of procedures providing that necessary and appropriate tests are carried out and that materials are not released for usage or products for sales or supplies until their quality is ascertained to be satisfactory.

Activities of Quality Control

Activities of Quality Control sector are as follows:

- Preparing of specifications and test methods for physical-chemical, microbiological and biological investigation of entering materials, intermediaries, semi-finished products and finished products and in-process control
- Validation of analytical methods
- Analysis of entering materials, intermediaries, semi-finished and finished products and in-process controls
- Approving or disapproving of entering materials, intermediaries, semi-finished and finished products
- Filing and recording of documentation for production and control
- Product stability follow up

The Quality Control is performed by Institute for Public Health of Republic of Macedonia, based on contract for cooperation.

C.8. DISTRIBUTION, CLAIMS AND WITHDRAWAL OF PRODUCTS

Storage and distribution

Finished goods are stored in Finished Goods Warehouse on pallets an sufficient distance from each other in order to avoid overcrowding, enable an easier requisition and cleaning, and to prevent confusion.
Temperature is monitored on everyday basis. Limit values are 15°C - 25°C.
Issuing of goods from the Warehouse is performed on the basis of delivery order - dispatch note. The dispatch note contains: order number, date, name and address of buyer, name of product, quantity, batch and way of dispatch.
Issuing of goods is performed according to *first in - first out principle*.
Delivery order represents at the same time the records on product distribution. One copy is distributed to Finished Goods Warehouse and kept there one year after expiry date for this product. Second copy of order is retained by buyer.

Claims

Procedures and responsibilities for handling the product claims in the market are described in accordance with standard operating procedure. Every claim must be investigated in details and objectively regardless its nature.

Recall of products

Mode of handling the product which is not meeting the specified quality and nevertheless found in the market and thus must be withdrawn from the market, is described in details in respective procedure. The procedure involves persons responsible for decisions on recall, reports and coordination of the recall.
Recall is done when quality of products (for example, composition, appearance, packaging, expiry date, etc.) does not comply with defined requirements according to information obtained on the basis of: postproduction inspection of drugs, claim of buyer, or any other external client.
The extent of recall (the whole shipment, part of shipment) depends on potential impact on health. The recall may be made from own warehouse, wholesaler, hospital storage, pharmacy or from individual user.
Decision on recall is taken by The General Manager.
Products withdrawn from the market are stored in separate dedicated area marked with *RECALLED PRODUCTS* and recall. Recalled products in all recalling phases must be handled in such a way not allowing for repeated distribution. Recalled products must be destroyed (transferred into Pharmaceutical waste storage). The documentation regarding decisions and execution of recall is kept. The period for keeping of documentation in recall is one year after expiry date of product being subject of the recall.

C.9 SELF INSPECTION

Internal inspection covers all activities inside and outside Inter-evrogeneks that can have impact on quality of product and level of fulfillment of GMP requirements, legal and other regulations related to drug manufacturers. Inspection areas are the areas foreseen in GMP, i.e.: personnel, areas, equipment, documentation, production, quality control, distribution of products, claims and recalls settlement, as well as inspection with raw materials suppliers and in-bulk product suppliers.

Internal inspection is carried out according to annual plan of internal inspection and exceptionally, it can be made upon request of General Manager.

Results of internal inspection are given in internal inspection reports. Reports on inspection including proposed corrective actions, terms and persons in charge, verified by internal inspector, are delivered to the company's General Manager. The report is sent not later than 20 days and in is a strictly confidential document of strictly limited circulation.

Internal inspector is liable to report annually on work of internal inspection, and it contains inspection frequency data and global conclusions, as well as proposal of corrective measures and proposal of activities on improvement.

Internal inspector is following up the advancement of actions for the purpose of corrective measures implementation.

LIST OF PRODUCTS

BRAND NAME	FORM
VARUMIN	solution
Glukonormin forte	tablets
Varuklim	tablets
Varuprostin	tablets
Varutensin	tablets
Paradental	solution
Varuhemoroidal	solution
Varumin herbal	tea
Glukonormin	tea
Varuklim	tea
Varuprostin	tea
Varutensin	tea
Varuascitofin	tea