MINISTRY OF PUBLIC HEALTH

ORDER
on approval of Regulations relating to the contract-based control of medicinal product quality, as drawn between the manufacturer and a control unit outside the manufacturing site, in case of certain special testing

Having regard of Law No. 95/2006 on healthcare reform, Title XVII, The Medicinal Product, and of Government Ordinance No. 125/1998 related to the set up, organisation and functioning of the National Medicines Agency, approved with changes and completions through Law No. 594/2002, with further changes and completions,

on seeing the Approval Report of the General Pharmaceutical and Medical Devices Directorate No. E.N. 2.142 of 17 July 2006,

based on Government Decision No. 862/2006 organisation and functioning of the Ministry of Public Health

The minister of public health hereby issues the following order:

Article 1. - The Regulations relating to the contract-based control of medicinal product quality, as drawn between the manufacturer and a control unit outside the manufacturing site, in case of certain special testing are approved, as provided in the annex, which is part of the present order.

Article 2. - The present order shall come into force on 28 July 2006.

Article 3. - The present order shall be published in the Official Gazette of Romania, Part I.

Minister of public health,
Gheorghe Eugen Nicolăescu

Bucharest, 17 July 2006.
No. 873.

ANNEX

REGULATIONS
relating to the contract-based control of medicinal product quality, as drawn between the manufacturer and a control unit outside the manufacturing site, in case of certain special testing

Article 1. - (1) To the purpose of the present regulations, the terms and concepts used herein shall mean as follows:

a) *control unit (testing unit)* - laboratory for physico-chemical, microbiological, biological etc. control, performing laboratory checks in view of grant of certificate of analysis, development of stability studies, elaboration of control methodologies etc.;

b) *off-manufacturing site control unit (independent control unit)* - control unit, distinct legal entity, contracting performance of test types provided for under a), on request.

(2) Present regulations do not apply to control laboratories which are part of the structure of a medicinal product manufacturing unit, which are authorised at the same time with the latter, according to Article 748 and the following articles of Law No. 95/2006 on healthcare reform, Title XVII, The Medicinal Product.

Article 2. - Based on Article 749 (1) c) of Law No. 95/2006, Title XVII, The Medicinal Product, medicinal products manufacturers/importers may contract special tests only to independent control unit authorised or acknowledged for their medicinal product control activity by the National Medicines Agency.

Article 3. - (1) Authorisation of independent control unit, herewith called *authorisation*, is granted by the National Medicines Agency in accord with provisions of Article 725 b) of Law No. 95/2006, Title XVII, The Medicinal Product, in result of application by the unit and is in force for 3 years.

(2) Authorisation is granted based on favourable inspection report by National Medicines Agency inspectors.

(3) In order to be granted authorisation, the applicant – a legal entity established in Romania, submits to the National Medicines Agency an application for schedule of inspection, in accord with the format given in Annex 1, accompanied by the following documents:

a) administrative documents:

- documents of company establishment (statutes and company contract);
- irrevocable decision of delegate-judge for authorisation and register of the company or, as the case may be, definitive court decision;
- copy of company registration with the Registry of Commerce, together with its annexes, and, if necessary, registration certificates with accompanying mentions;
- ownership of the company area/areas;

b) technical documents:

- standard dossier of the independent control unit, as given in Annex 2.

Article 4. – Authorisation of independent control unit that are legal entities established in the European Union or the European Economic Area (EEA) is acknowledged by the National Medicines Agency based on proof of respective authorisation for medicinal product control activity by the competent authority in the field in the country of origin; Article 3 (3) provisions shall be applied in case of lack thereof.

Article 5. - No longer than 10 days as of registration of the application, the National Medicines Agency provides a response to the Applicant on documents submitted in view of inspection:

a) should the submitted dossier comply with provisions of Article 3 (3) of these regulations, the applicant is notified on acceptance of the application for inspection and on inspection fee as approved through order of the minister of public health, which is to be paid longer than 10 days as of receipt of the NMA notification, devised according to the format given in Annex 3; inspection is to occur no longer than 10 days as of confirmation of payment, on a date to be set in agreement with the applicant;

b) should the submitted dossier be incomplete, the applicant is notified on information to be submitted to the National Medicines Agency, according to the format given in Annex 4; in such cases, enter into force of the deadline is suspended not longer than provision of the complete dossier.

Article 6. - Inspection is performed in keeping with an inspection plan set up by the inspector appointed by the National Medicines Agency, which plan is sent to the applicant at least minimum 3 days prior to the inspection date.

Article 7. - Inspection in view of independent control unit authorisations checks compliance with provisions for control of medicinal product quality of Principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use, approved through order of the minister of public health, and of the Guideline for inspection of laboratories for quality physico-chemical control, approved through decisions of the Scientific Council of the National Medicines Agency.

Article 8. - Inspection is concluded with an inspection report to be sent to the applicant no later than 20 days as of inspection performance:

a) in case of favourable inspection report, authorisation of the independent control unit is granted by the National Medicines Agency no longer than maximum 90 days as of registration by the applicant of the complete dossier

b) follow up of resolution of certain possible deficiencies found (major, other deficiencies) is made after grant of authorisation;

c) in case of unfavourable inspection report, the unit in question may apply for a new inspection after resolution of deficiencies found.

Article 9. - Authorisation of the independent control unit is granted un the format given in Annex No. 5, in two original copies, one of which is handed to the applicant unit, the other to be retained by the National Medicines Agency – the Pharmaceutical inspection department.

Article 10. - (1) New authorisation of independent control units established in Romania, whose authorisations were in force on the date of Law No. 95/2006, title XVII, The Medicinal Product coming into force is granted based on a statement that no changes have been made to documents submitted for the purpose of the previous authorisation, with preservation of the same term of validity as that of the previous authorisation, which shall be withdrawn.

(2) If changes have been made to the above mentioned documents, the applicant has the obligation to submit a complete dossier according to provisions of Article 3 (3) no longer than two months since entry into force of Law No. 95/2006, Title XVII, The Medicinal Product.

(3) Authorisations of independent control units granted by the National Medicines Agency are no more in force after maximum 3 months as of coming into force of Law No. 95/2006, Title XVII, The Medicinal Product.

(4) 90 days prior to expiry of the deadline provided in Article 3 (1), the independent control unit submits to the National Medicines Agency the documents mentioned under Article 3 (3).

Article 11. – Any change introduced after grant of the authorisation is first notified to the National Medicines Agency, at the same time with application for a new authorisation; depending on the nature of the change (administrative and/or technical), the authorisation is granted based on the updated dossier submitted or based on a new favourable inspection report.

Article 12. – Loss of authorisation incurs annulment thereof and grant of a new authorisation is made based on the following documents:

- application submitted according to the format provided in Annex 6;
- proof of loss publication in a widely circulated newspaper;
- copies of documents submitted together with the initial authorisation dossier;
- statement that no changes have been made to the information that have initially allowed authorisation for manufacture/importation.

Article 13. - (1) Should changes occur of one or several of the conditions underlying grant of authorisation, the National Medicines Agency shall suspend or withdraw authorisation of the independent control unit, under which circumstances the manufacturer/importer may no more make use of the control services provided by the control unit in question. After such authorisation suspension or withdrawal, the National Medicines Agency certificate of analysis for a manufacturer/importer is rendered void.

(2) In case the unit ceases its activity, its authorisation shall be withdrawn an application shall be submitted to the National Medicines Agency in that respect, the National Medicines Agency, under which circumstances the manufacturer/importer may no more make use of the control services provided by the control unit in question.

Article 14. - (1) The contract concluded between the manufacturer/importer (contract provider) and the independent control unit (contract beneficiary), referred to under Article 2 is ended according to provisions of chapter XIII " Contracted out activities" of Principles and guidelines of good manufacturing practice in respect of

medicinal products for human use and investigational medicinal products for human use, approved through order of the minister of public health.

(2) The contract is submitted to the National Medicines Agency - the Pharmaceutical inspection department for verification in view of approval.

(3) Any change in contract terms introduced after such approval makes the object of an additional document to be submitted to the National Medicines Agency - the Pharmaceutical inspection department for verification in view of approval

Article 15. - Annexes 1 - 6 are an integral part of these regulations.

Annex No. 1

To
THE NATIONAL MEDICINES AGENCY
Pharmaceutical inspection department

The undersigned ....., representative of (name and surname) ……..., hereby apply for scheduling an inspection at the site of the unit in view of authorisation of the independent control unit for control of medicinal products for human use.

Please find attached to the present application the documentation required under Article 3 (3) of Order of the minister of public health no. 873/2006 regarding approval of Regulations relating to the contract-based control of medicinal product quality, as drawn between the manufacturer and a control unit outside the manufacturing site, in case of certain special testing.

Signature, stamp
.....

Annex No. 2

STANDARD DOSSIER OF THE INDEPENDENT CONTROL UNIT

Filling in this form is devised to provide minimal information required on the control site to be inspected.

Form No. 1: Information on the control unit

1. General information
2. Activities relevant for the National Medicines Agency
3. Control sites
4. Responsible persons and control unit management team

Form No. 2: Information on the control unit

CHAPTER 1: General information

1.1. General issues

1.2. Activities involving control of authorised medicinal products for human use

1.3. Types of activities involving control of medicinal product

1.4. Products checked at the unit site, other than medicinal products

CHAPTER 2: Personnel and quality management

2.1. Personnel working at the respective control site

2.2. Key personnel and organisational chart

2.3. Quality management system

2.4. Annual training plan

2.5. Requirements regarding personnel health and hygiene

CHAPTER 3: *Buildings and equipment*

3.1. Blueprints

3.2. Sites (buildings, areas, finishing)

3.3. Air conditioning and ventilation systems, characteristics for clean rooms, qualifications

3.4. Handling of very toxic, hazardous, sensitising agents and drugs and psychotropes or live organisms

3.5. Water treating systems, qualifications

3.6. Control equipment, qualifications

3.7. Maintenance and calibration

CHAPTER 4: Dossier

4.1. General issues

4.2. Information systems

4.3. Main procedures or procedure groups

CHAPTER 5: Medicinal product for human use quality control

5.1. Brief outline of activities performed

5.2. Operations involving handling of reagents and test samples

5.3. Products for which non-compliant certificate of analysis have been released during the previous two years

5.4. Validated control methods

5.5. Out-of-specifications outcomes

CHAPTER 6: Release of certificate of analysis and control reports

CHAPTER 7: Contracts for quality control of medicinal products for human use

7.1. Contracted out control activities

7.2. Contracted control activities for third parties

7.3. Other contracted or sub-contracted activities

CHAPTER 8: Complaints

8.1. Procedures, records, registration related to resolution of complaints from contract providers

CHAPTER 9: Inspections by competent authorities and internal audits

9.1. Inspections conducted by national authorities (over the past 5 years)

9.2. Inspections conducted by foreign authorities (over the past 5 years)

9.3. Internal audits performed in the previous year

CHAPTER 10: Methods used at control site

FORM NO. 1: INFORMATION ON CONTROL UNIT

1. GENERAL INFORMATION

a. Name of the unit, as registered with the legal authority (independent control unit)

b. Legal entity/juridical form

c. Address, telephone and fax numbers of the central site

2. ACTIVITIES RELEVANT FOR THE NATIONAL MEDICINES AGENCY

In the table below, please tick areas according to activities performed by the unit (no details are needed); the date when the authorisation was granted should be provided in case an authorisation is in place.

Control activities	Medicinal products for human use	Investigational medicinal products for human use	Medicinal products for veterinary use	Products**
- starting materials				
- finished products				
- packaging materials				
Stability studies				
Control methodologies				
Other activities*				

* Other activities, if relevant.
** Important products:
- Medical devices
- Cosmetic and hygiene products
- Dietetic products, food supplements
- Laboratory reagents
- Other

3. CONTROL SITES

Please fill in the table below:

Control sites	Address	Telephone/Fax number	Activities performed (according to pct. 2)	Authorisation granted
.../…				

Notice: A No. 2 Form should be filled in for each check at the site of an independent control unit.

4. RESPONSIBLE PERSON(S) AND THE CONTROL UNIT MANAGEMENT TEAM

Responsible and management persons	Name, surname	Work place	Position	Tel./Fax
Control unit Independent Director				
Quality insurance Responsible person				
Quality control Responsible person				
Quality control Responsible person alternate				
Technical/Maintenance Responsible person				

FORM NO. 2: INFORMATION ON CONTROL SITE

CHAP. 1 GENERAL INFORMATION

1.1. General issues

a. Name of the control site

b. Telephone (24/24 h) and Fax

c. Full regular mail address

1.2. Activities involving control of authorised medicinal products for human use

a. Documents and date of issuance (please attach a copy of authorisation in force and annexes);

b. Any other activities authorised at the respective control site

c. In case of units under environment/hazard protection legislation, please attach documents.

1.3. Types of activities involving control of medicinal product

Type of activity	Medicinal product for human use	Starting material	Packaging materials
Physicochemical control			
Biological, microbiological control			
Stability studies			
Control methodologies			

1.4. Products testate in the unit other than medicinal products

The table below should only be filled in case the products are tested in the same work areas as the medicinal products, starting materials and packaging materials for medicinal products for human use.

Category	Control activity
Medical devices	
Cosmetic and hygiene products	
Dietetic products, food supplements	
Laboratory reagents	
Products	

CHAPTER 2: PERSONNEL AND QUALITY MANAGEMENT

2.1. Personnel working at the respective control site, participating in activities involving control (according to case).

Notice: The table below should be filled in also including part-time employees.

Activity	Number of employees
Quality insurance	
Quality control	
- Physic-chemical - Biological, microbiological	
Technical/Maintenance	
Goods purchased	
Total	

2.2. Key personnel and organisational chart

a. Organisational chart for Quality insurance and Quality control (please name key persons in each activity sector).

b. Key positions: Please fill in the table below, naming heads of activity sectors mentioned above.

Name, surname	Position	Work experience	Education
Quality control responsible person			
Quality insurance responsible person			
Technical/ Maintenance Responsible person			
Responsible person for activity involving drugs and psychotropes			

2.3. Quality management system

Please provide brief outline (not more than 200 words/half an A4 format page) of quality management system of the unit.

2.4. Annual training plan

Type of training	Number of employees involved	Number of hours	Training site - within the unit - outside the unit
Basic training			
In-service training			
Ongoing training			

The table below should be followed by a brief outline (not more than 100 words – a quarter of an A4 format page) of the evaluation of training efficiency.

2.5. Requirements concerning personnel health and hygiene

The table below should be filled in with information on the protection equipment available (please specify the type of footwear, mask, gloves, eye protection etc.)' if needed, please give details on equipment cleaning/sterilisation (on check/contract site):

Protection equipm. for / Activities	Feet	Body	Hands	Head
Physicochemical control				
Biological, microbiological control				
Other				

Please provide brief outline (100 words) of checks performed on health of control involved personnel: procedures, individual medical records, units providing medical services.

CHAPTER 3. BUILDINGS AND EQUIPMENT

3.1. Blueprints

NOTICE: Blueprints should be numbered, and include orientation and scale.

All blueprints should be presented on A4 paper (A3 only if necessary). A brief (100 de words, 1/4 of A_4) description of surroundings and other industrial activities in the area should be provided only if relevant.

a. General location of activities involving control (please indicate additional activities and the general blueprint of control areas)

b. Simple plan of buildings where control activities are performed.

Please indicate areas dedicated to the various activities, such as: reception, sampling, Physicochemical/biological, microbiological control, stability studies, archiving, storing, offices etc.

Please indicate sites/buildings and specify when they were built.

c. Blueprints for each site, floor-by-floor (if several floors are involved).

A reference code should be used for each control installation or equipment, which should be introduced in the tables below.

If necessary, one blueprint per room should be provided for clean areas. Such blueprints should indicate rate relative pressures, number of air exchanges/hour and air flow directions.

d. Simple plans for personnel, materials and activities flows.

Please use arrows in various colours to highlight access and sample, materials and personnel routes.

3.2. Sites (buildings, areas, finishing)

Local	Room: name, blueprint reference	Area	Operations performed	IVAC Reference (if necessary)
…/…				

For clean areas only:

Room: name, blueprint reference	Area	Operations performed	Finishing		
			Floor	Walls	Ceiling
…/…					

3.3. Air conditioning and ventilation systems, characteristics for clean rooms, qualifications

Please provide necessary data on installations required to insure heating, ventilation and exhaust.

a. In the table below, please include IVAC components and operation parameters as approved in the plan (if necessary).

Type of unit IVAC (UTA)	Air volume mc/h and % recirculation	Efficiency %			Number of air exchanges/h for each AHU	Buildings protected by each AHU
		Stage 1	Stage 2	Stage 3		
…/…						

b. For clean buildings only:

Building	Class B.P.F	Air exchanges/h	Activity	Relative pressure	IVAC Reference
…/…					

c. Qualifications system – Please tick the appropriate box:

Plan qualification (CPr) YES □ NO □

Qualification on installation (CI) YES □ NO □

Operation qualification (CO) YES □ NO □

Performance qualification(CP) YES □ NO □

d. Please specify the testing laboratory which has performed the qualifications system.

The testing laboratory is certified by the national authority in the field?

YES □ NO □

3.4. Handling of very toxic, hazardous, sensitising agents and drugs and psychotropes or live organisms

If relevant, please give brief outline of specific endowments for activities involving very active products.

If necessary, please mention handled products (DCI and therapeutic group) and give brief outline of organisation of activities with respective products.

3.5. Water treatment systems (only for water used in control activities mentioned under 1.3) qualifications.

a. Please devise the diagram of each water treatment system and should be fill in the table below:

Water quality	Type of installation (mechanism)	Capacity	Number of samples	Sampling frequency	Sanitising frequency
Drinking water					
Purified water					
Highly purified water					

b. Water system qualifications - Please tick the appropriate box:

Plan qualification (CPr) YES □ NO □
Qualification on installation (CI) YES □ NO □
Operation qualification (CO) YES □ NO □
Performance qualification(CP) YES □ NO □

c. Please specify the testing laboratory which has performed the qualifications system.

The testing laboratory is certified by the national authority in the field?
YES □ NO □

3.6. Control equipment, qualifications

a. Please fill in the table below with main equipment used in laboratory checks:

Location (ref. to plan)	Name of the equipment	Installation year
…/…		

b. Qualifications of each declared control equipment - Please tick the appropriate box:

Plan qualification (CPr) YES □ NO □
Qualification on installation (CI) YES □ NO □
Operation qualification (CO) YES □ NO □
Performance qualification(CP) YES □ NO □

c. Please specify the unit which has performed equipment qualifications.

3.7. Maintenance and calibration

Please fill in the table below:

Programmes for:	A plan is in place for de calibrations and records	A plan is in place for preventive/curative maintenance and records	Unit, calibration responsible person	Unit, maintenance responsible person

Utilities (IVAC components, water installation				
Control equipment				

CHAP. 4 DOSSIER

4.1. General issues

Please give brief outline (not more than 200 words/half a A4 format page) of rules for dossier set up, revision and distribution requested for development of all activities at the respective control site.

4.2. Information systems

Please fill in the table below in relation to information systems relevant for the GPx field (GMP, GLP, GLAP etc.):

Information system in use (software)	**Scope**	**Installation date**	**Validation date**	**Degree of risk (based on risk assessment):** **- critical** **- non-critica**
…/…				

4.3. Main procedures or procedure groups:

Please list general and specific procedures (and respective reference numbers) set up for the inspected control site.

CHAP. 5 MEDICINAL PRODUCT FOR HUMAN USE QUALITY CONTROL

5.1. Brief outline of activities performed

Please provide brief outline (200 words / 1/2 A4page) of quality control diagrams and specific procedures in use.

Please fill in the table below:

Product/Activity category	**Name/position of persons in charge of Physicochemical testing**	**Name/position of persons in charge of biological, microbiological testing**
Starting materials		
Packaging materials		
Medicinal products (finished products, bulk products)		
Stability studies		
Control methodologies		

5.2. Operations for handling of reagents and test samples

Please fill in the table below.
If necessary, a brief outline of these operations may be added (not more than 200 words/half an A4 format page).

Operation	Person in charge	Remarks
Sample reception		
Reagents reception		
Sampling		
Control activities performed - Physicochemical - biological, microbiological		
Stability studies (protocol elaboration, trial conduct, final trial reports)		
Calibrations, equipment qualifications		
Methods validations		
Issuance of documents supporting quality of controlled products		
Documents keeping/Archiving		

5.3. Products for which non-compliant certificate of analysis have been released during the previous two years

Please fill in the table below:

Product	Total number of batches received	Noncompliant batches
Starting materials		
Packaging materials		
Medicinal products (bulk product finished product)		

5.4. Validated control methods

Please fill in the table below:

Reference to validation report	Name of the method	Product(s)involved	Date of validation report
…/…			

5.5. Out-of-specifications outcomes

Please fill in the table below:

Type of product/starting material/packaging material/medicinal product	Cause

CHAP. 6 RELEASE OF CERTIFICATE OF ANALYSIS AND CONTROL REPORTS

Please fill in the table below:

Product category	**Name/Position of persons responsible for release of certificate of analysis, trial reports**	**Name/Position of responsible persons alternates delegated for release of certificate of analysis, trial reports**
Starting materials		
Packaging materials		
Medicinal products (bulk)		
Medicinal products (finished products)		
Control methodologies		
Stability studies (protocols, reports)		

CHAP. 7 CONTRACTS FOR QUALITY CONTROL OF MEDICINAL PRODUCTS FOR HUMAN USE

7.1. Contracted out control activities

Contract beneficiary*	**Object of the contract (products included)**	**Analysis(es) under contract**	**Number and date of running contract**	**Date of latest provider audit of contract beneficiary**
…/…				

7.2. Contracted control activities for third parties

Contract provider*	**Object of the contract (products included)**	**Analysis(es) under contract**	**Number and date of running contract**
…/…			

7.3. Other contracted and subcontracted activities - if relevant.

CHAPTER 8: COMPLAINTS

8.1. Procedures, records, registration of resolution of complaints from contract providers

Please provide brief outline (200 words/1/2 A4 format page) of resolution of complaints, and the final decisions which the independent control unit may make.

CHAPTER 9: Inspections by competent authorities and internal audits

9.1. Inspections conducted by national authorities (over the past 5 years)

* according to GMP Guideline definitions.

Date(s) inspection/inspections	Inspector's/inspectors' name(s)	Grounds for inspection
…/…		

9.2. Inspections conducted by foreign authorities (over the past 5 years)

Date(s) inspection/inspections	Authority/Organisation	Grounds for inspection
…/…		

9.3. Internal audits performed in the previous year

Date(s)	Object of internal audit	Remarks
…/…		

CHAPTER 10: METHODS USED AT CONTROL SITE

Please tick methods used at the control site in the list below.

1. Physical, Physicochemical and chemical methods

1.1. Physical methods □
- 1.1.1. Refraction index □
- 1.1.2. Boiling point □
- 1.1.3. Melting point □
- 1.1.4. Dropping point □
- 1.1.5. Solidification point □
- 1.1.6. Distillation interval □
- 1.1.7. Viscosity □
- 1.1.8. Relative density □
- 1.1.9. Rotatory power □
- 1.1.10. Determination of strength in alcohol □
- 1.1.11. Other methods <please fill in> □

1.2. Physicochemical methods
- 1.2.1. Solubility □
- 1.2.2. Solution aspect and coloration □
- 1.2.3. Polarography □
- 1.2.4. Loss through drying □
- 1.2.5. Residue through calcination □
- 1.2.6. pH determination □
- 1.2.7. Water determination □
- 1.2.8. Potentiometric dosage □
- 1.2.9. Other methods <please fill in> □

1.3. Chemical methods
- 1.3.1. Indices □
  - 1.3.1.1. Acidity index □

1.3.1.2. Ester index □
1.3.1.3. Hydroxyl index □
1.3.1.4. Ester index □
1.3.1.5. Peroxide index □
1.3.1.6. Saponification index □
1.3.2. Non-saponifiable substances □
1.3.3. Control of inorganic impurity limits □
1.3.4. Control of limits for easily charring organic substances □
1.3.5. Metoxi-group dosage □
1.3.6. Nitrogen determination in organic combinations □
1.3.7. Mineralisation of organically linked halogens and sulphur □
1.3.8. Other methods <please fill in> □

2. Instrumental methods □
2.1. Spectrophotometry □
2.1.1. Spectrophotometric identification in UV and visible □
2.1.2. Spectrophotometric identification in infrared □
2.1.3. Atomic absorption spectrophotometry □
2.1.4. Other methods <please fill in> □
2.2. Chromatography □
2.2.1. Paper chromatography □
2.2.2. Thin layer chromatography □
2.2.3. Gas chromatography □
2.2.4. Pressurised liquid chromatography □
2.2.5. Other methods <please fill in> □

3. Pharmacotechnical methods □
3.1. Disaggregation □
3.2. Dissolution □
3.3. Other methods <please fill in> □

4. Pharmacognostic methods □
4.1. Saturation factor of plant products □
4.2. Bitterness index □
4.3. Dosage of haemolytic saponine in plant products □
4.4. Dosage of soluble substances in plant products □
4.5. Dosage of tannins in plant products □
4.6. Dosage of volatile oils in plant products □
4.7. Other methods <please fill in> □

5. Biological and biochemical methods □
5.1. Biological, microbiological □
5.1.1. Sterility control □
5.1.2. Microbial contamination □
5.1.3. Antimicrobial preservatives efficacy control □

5.1.4. Microbiological activity of antibiotics □
5.1.5. Pyrogenic impurities □
5.1.6. Toxic impurities □
5.1.7. Other methods <please fill in> □

5.2 Biochemical

5.2.1. Seric proteins identification through double diffusion in gel □
5.2.2. Chemotripsine enzymatic activity □
5.2.3. Pancreatine enzymatic activity □
5.2.4. Pepsine enzymatic activity □
5.2.5. Tripsine enzymatic activity □
5.2.6. Vasopressor activity □
5.2.7. Hypotensive impurities □
5.2.8. Other methods <please fill in> □

ABBREVIATIONS:

IVAC = Heating, ventilation, air conditioning system
UTA = Unit for air treatment
BMP = Good Manufacturing Practice
BLP = Good Laboratory Practice
BALP = Good Analytic Laboratory Practice

Annex No. 3

MINISTRY OF PUBLIC HEALTH
THE NATIONAL MEDICINES AGENCY

To
.....

We hereby inform you that, following study of the dossier submitted to the National Medicines Agency, you application for an inspection in view of independent control unit authorisation has been approved.
Therefore, in accord with regulations in force on National Medicines Agency tariffs, we would like you to pay the ……. tariff due for inspection in no longer than 10 working days.

Inspection is due no longer than 10 days as of confirmation of payment, on a jointly agreed date.

President, *Head of the Pharmaceutical inspection Department,*
..... ……

Annex No. 4

MINISTRY OF PUBLIC HEALTH
THE NATIONAL MEDICINES AGENCY

To

.....

In view of preparation of the inspection at …….. for ……., we would like you to also submit the documents and information: **.....**

Should the submitted documents and information provide sufficient data on the requested inspection, we will approve your application and inform you on the inspection fee to be paid to the National Medicines Agency account, according to regulations with regulations in force on National Medicines Agency tariffs.

President, ...

Head of the Pharmaceutical inspection Department, …….....

Annex No. 5

Independent control unit authorisation
FORM

1. Number of authorisation
2. Name/Name authorisation holder
3. Address(es) of site(s) to be controlled (Please list all authorised sites except when authorised separately).
4. Authorisation holder offices
5. Domain of the authorisation:

Annex No. 1 to independent control unit authorisation (Separate annexes to be issued for each control site.)

6. Legal basis of authorisation
7. Name of the responsible person of the National Medicines Agency (competent authority of Romania granting authorisation to the independent control unit)
8. Signature
9. Date
10. Annexes:

- Annex No. 1;
- Annex No.2 (addresses of laboratories contracting performance of certain special tests for the independent control unit authorisation holder);
- Annex No.3 (name of quality control responsible persons);
- Annex No. 4 (date of the inspection based on which authorisation has been granted; the domain covered by the latest inspection).

Annex No. 6

To
THE NATIONAL MEDICINES AGENCY
Pharmaceutical inspection department

The ....., established in …....., Address …....., Telephone/Fax number ....., registered with the Registry of Commerce under....., fiscal code....., represented by .....,
(name and surname)
position ....., in accord with Article 10 of Regulations relating to the contract-based control of medicinal product quality, as drawn between the manufacturer and a control unit outside the manufacturing site, in case of certain special testing, approved through Order of the minister of public health No. 873/2006, hereby applies for grant of a new authorisation.

We hereby attach the proof of notification on loss of independent control unit authorisation in .....
(name of the newspaper)

Signature and stamp

…….

Annex No. 1
to independent control unit authorisation

DOMAIN COVERED BY THE LATEST INSPECTION
(Please erase not applicable sections or use YES/NO)
Name and address of the site:

□ Medicinal products for human use □ Starting materials □ Packaging materials

TESTING ACTIVITIES
□ Physical, physico-chemical tests and instrumental analyses (according to Part 1) □ Biological, microbiological tests (according to Part 2) □ Testing medicinal product stability (according to Part 3) □ Other activities (according to Part 4) < please fill in>

Part 1 PHYSICAL, PHYSICO-CHEMICAL TESTS AND INSTRUMENTAL ANALYSES	
1.1	**Physical, physico-chemical and chemical methods**
	1.1.1. Physical methods 1.1.1.1. Refraction index 1.1.1.2. Boiling point 1.1.1.3. Melting point 1.1.1.4. Dropping point 1.1.1.5. Solidification point 1.1.1.6. Distillation interval 1.1.1.7. Viscosity 1.1.1.8. Relative density 1.1.1.9. Rotatory power 1.1.1.10. Determination of strength in alcohol 1.1.1.11. Other methods <please fill in>
	1.1.2. Physicochemical methods 1.1.2.1. Solubility 1.1.2.2. Solution aspect and coloration 1.1.2.3. Polarography 1.1.2.4. Loss through drying 1.1.2.5. Residue through calcination 1.1.2.6. pH determination 1.1.2.7. Water determination 1.1.2.8. Potentiometric dosage 1.1.2.9. Other methods <please fill in>

	1.1.3. Chemical methods 1.1.3.1. Indices 1.1.3.1.1. Acidity index 1.1.3.1.2. Ester index 1.1.3.1.3. Hydroxyl index 1.1.3.1.4. Ester index 1.1.3.1.5. Peroxide index 1.1.3.1.6. Saponification index 1.1.3.2. Non-saponifiable substances 1.1.3.3. Control of inorganic impurity limits 1.1.3.4. Control of limits for easily charring organic substances 1.1.3.5. Metoxi-group dosage 1.1.3.6. Nitrogen determination in organic combinations 1.1.3.7. Mineralisation of organically linked halogens and sulphur 1.1.3.8. Other methods <please fill in>

1.2.	**Instrumental methods**
	1.2.1. Spectrophotometry 1.2.1.1. Spectrophotometric identification in UV and visible 1.2.1.2. Spectrophotometric identification in infrared 1.2.1.3. Atomic absorption spectrophotometry 1.2.1.4. Other methods <please fill in>
	1.2.2. Chromatography 1.2.2.1. Paper chromatography 1.2.2.2. Thin layer chromatography 1.2.2.3. Gas chromatography 1.2.2.4. Pressurised liquid chromatography 1.2.2.5. Other methods <please fill in>
1.3.	**Pharmacotechnical methods**
	1.3.1. Disaggregation 1.3.2. Dissolution 1.3.3. Other methods <please fill in>
1.4.	**Pharmacognostic methods**
	1.4.1. Saturation factor of plant products 1.4.2. Bitterness index 1.4.3. Dosage of haemolytic saponine in plant products 1.4.4. Dosage of soluble substances in plant products 1.4.5. Dosage of tannins in plant products 1.4.6. Dosage of volatile oils in plant products 1.4.7. Other methods <please fill in>

Any restrictions or remarks to clarify the domain covered by the above testing activities

Part 2 BIOLOGICAL, MICROBIOLOGICAL TESTS	
2.1.	**Biological, microbiological and biochemical methods**
	2.1.1. Biological, microbiological 2.1.1.1. Sterility control 2.1.1.2. Microbial contamination 2.1.1.3. Antimicrobial preservatives efficacy control 2.1.1.4. Microbiological activity of antibiotics 2.1.1.5. Pyrogenic impurities 2.1.1.6 Toxic impurities 2.1.1.7. Other methods <please fill in>
	2.1.2. Biochemical 2.1.2.1. Seric proteins identification through double diffusion in gel 2.1.2.2. Chemotripsine enzymatic activity 2.1.2.3. Pancreatine enzymatic activity 2.1.2.4. Pepsine enzymatic activity 2.1.2.5. Tripsine enzymatic activity 2.1.2.6. Vasopressor activity 2.1.2.7. Hypotensive impurities 2.1.2.8. Other methods <please fill in>

Any restrictions or remarks to clarify the domain covered by the above testing activities .....

Part 3 TESTING MEDICINAL PRODUCT STABILITY	
3.1.	**Stability in normal conditions**
3.2.	**Stability in accelerated conditions**
3.3.	**Photostability**

Any restrictions or remarks to clarify the domain covered by the above testing activities .....

Part 4 OTHER ACTIVITIES (please fill as necessary)	
4.1.	
4.2.	
4.3.	
....	

Any restrictions or remarks to clarify the domain covered by the above testing activities.....

Annex No. 2
to independent control unit authorisation

Address/Addresses of laboratories contracting performance of certain special tests for the independent control unit authorisation holder:…….....
……

Annex No. 3
to independent control unit authorisation

Name of person/of quality control responsible persons:
……
…….

Annex No. 4
to independent control unit authorisation

Date of the inspection based on which authorisation has been granted:

……

(day, month, year)

Domain covered by the latest inspection:

……..…….....**.....**