

A. Proiecte CEEEX 2005 si CEEEX 2006

1. CEEEX 2005 Modul I

Titlul proiectului: "Adaptarea si standardizarea unor metode de analiza conform directivelor europene, pentru controlul calitatii unor produse biotehnologice utilizate in terapia bolilor de nutritie si dieta"

„The adaptation and standardization of some methods of analysis according to the UE Directives, for the quality control of biotechnological products used in the therapy of nutrition and diet diseases”

Acronim: SMAPB

Nr.propunere: 282

Nr.contract: 26 / 10.10.2005

Perioada de desfasurare: 2005 – 2008

Parteneri:

P2 → Centrul de Biochimie Aplicata si Biotehnologie (Biotehnol)

P3 → Universitate de Medicina si Farmacie « Carol Davila »- Facultatea de Farmacie

P2 → The Applied Biochemistry and Biotechnology Center - Biotehnol

P3 → University of Medicine and Pharmacy “Carol Davila” - Faculty of Pharmacy

Coordonator de proiect : P1 – CO → Institutul National de Cercetare – Dezvoltare Chimico – Farmaceutica ICCF – Bucuresti

P1 – CO → National Institute for Chemical & Pharmaceutical Research & Development

Director de proiect : Dr.Chim. Sultana NITA

Rezumat:

Interesul crescand referitor la interdependenta alimentatie - sanatate a condus la studierea interdisciplinara a unor produse bioactive in domeniul bolilor de nutritie si dieta, dar mai ales al prevenirii instalarii acestora. In cazul cercetarilor biotehnologice si farmacologice efectuate pe plan mondial, un loc aparte il ocupa studiile referitoare la substantele active si produsele naturale obtinute din plantele recomandate in alimentatia antidiabetica, contra obezitatii, antispastica, dietetica.

Pentru folosirea rationala a plantelor medicinale in terapia naturista este importanta cunoasterea compozitiei lor chimice, a concentratiilor substantelor active, a modului de preparare si de administrare .

Prezentul proiect isi propune elaborarea si validarea unor metode prin tehnici avansate de analiza (GC, HPLC, HPTLC, AAS, UV-VIS) pentru controlul si asigurarea calitatii substantelor active si produselor obtinute prin biotehnologii cu actiune antidiabetica, contra obezitatii, antispastica, dietetica, precum si intocmirea standardelor de calitate si armonizarea lor in vederea integrarii europene. Prin precizia si selectivitatea crescuta, metodele elaborate vor permite evaluarea performanta a caracteristicilor principiilor active si a produselor de origine naturala obtinute, in conditiile unui pret competitiv si a respectarii standardelor de siguranta. De asemenea metodele elaborate vor permite un control eficient al procesului de fabricatie pe faze tehnologice in scopul alegerii parametrilor optimi de obtinere a produselor cu o productivitate crescuta.

The increasing interest for the interdependency between nutrition and health has led to the interdisciplinary study of some bioactive products in the field of nutrition and diet diseases, but most of all their prevention. In the case of biotechnological and pharmaceutical research conducted world-wide, the studies of active substances and natural products obtained from recommended plants have a leading role in the anti diabetic, against obesity, anti spastic and dieting nutrition.

For the rational using of the medicinal plants in the natural therapy, is important the knowledge of their chemical composition, of their concentration of the active substances, of their preparation and administration.

This project proposes to create and validate some methods through advanced analyzing techniques (GC, HPLC, HPTLC, AAS, UV-VIS) for the control and insurance of quality of the active substances and the products obtained through biotechnologies with anti diabetic, anti spastic, against obesity and dieting action, and to create the quality standards and to harmonize them for the European integration. Through precision and selectivity increased the methods we elaborated will allow the precise evaluation of the characteristics of the active principles and of the natural products obtained in the conditions of a competitive price while respecting the safety standards. Furthermore the elaborated methods will allow a efficient control of the fabrication process with it's different technological steps with the purpose of choosing the optimal parameters that will lead to the getting of products with increased productivity.

Plan de realizare – obiective:

Anul 2005

Etapa I (septembrie– decembrie)

Studiul documentelor privind cerintele nationale si europene referitoare la aplicarea unor tehnici moderne (HPLC, HPTLC, GC, AAS, UV-VIS) pentru controlul si asigurarea calitatii unor substante active in terapia bolilor de nutritie si dieta

I.1. Analiza datelor privind controlul unor compusi din clasa saponine triterpenice

I.2. Analiza datelor privind controlul unor compusi din clasa principii amare

I.3. Studii documentare privind validarea metodelor conform Directivelor Europene

I.4. Studii documentare privind prepararea unor produse bioactive de origine vegetala, recomandate in terapia bolilor de nutritie si dieta

Anul 2006

Etapa II (ianuarie- iunie)

Elaborarea si validarea conform Directivelor Europene, a unor metode de analiza pentru controlul calitatii unor compusi din clasa saponine triterpenice si experimentarea lor pe produse biotehnologice

II.1. Studii experimentale privind elaborarea unor metode pentru controlul calitatii unor compusi din clasa saponine triterpenice.

II.2. Studii experimentale pentru validarea metodelor elaborate

II.3. Studii experimentale privind validarea metodelor pentru produse biotehnologice

II.4. Obtinerea unor probe experimentale din *Glycyrrhizae glabra*

II.5. Aplicarea metodelor validate pentru dozarea unor saponine triterpenice din probe experimentale obtinute din *Glycyrrhizae glabra*

Etapa III (iulie - decembrie)

Elaborarea si validarea conform Directivelor Europene, a unor metode de analiza pentru controlul calitatii unor compusi din clasa principii amare si experimentarea lor pe produse biotehnologice

III.1. Studii experimentale privind elaborarea unor metode pentru controlul calitatii unor compusi din clasa principii amare

III.2. Studii experimentale pentru validarea metodelor elaborate

III.3. Obtinerea unor probe experimentale din *Taraxacum officinale*

III.4. Aplicarea metodelor validate pentru dozarea unor principii amare din probe experimentale obtinute din *Taraxacum officinale*

Anul 2007

Etapa IV (ianuarie- iunie)

Elaborarea si validarea conform Directivelor Europene, a unor metode de analiza pentru controlul calitatii unor compusi din clasa aminoacizilor si experimentarea lor pe produse biotehnologice

IV.1. Studii experimentale privind elaborarea unor metode pentru controlul calitatii unor compusi din clasa aminoacizilor

IV.2. Studii experimentale pentru validarea metodelor elaborate

IV.3. Studii experimentale privind validarea metodelor pentru produse biotehnologice

IV.4. Obtinerea unor probe experimentale din *Phaseolus vulgaris*

IV.5. Aplicarea metodelor validate pentru dozarea unor aminoacizi din probe experimentale obtinute din *Phaseolus vulgaris*

IV.6. Disiminarea informatiilor prin comunicare / publicare

Etapa V (iulie - decembrie)

Elaborarea standardelor (specificatiilor de calitate) in conformitate cu reglementarile europene

V.1. Elaborarea specificatiei de calitate pentru produse bioactive cu *acid glicirizic*

V.2. Elaborarea specificatiei de calitate pentru produse bioactive cu *principii amare*

V.3. Elaborarea specificatiei de calitate pentru produse bioactive cu *aminoacizi*

V.4. Elaborarea de lucrari stiintifice

Anul 2008

Etapa VI (ianuarie- iunie)

Transfer tehnologic si elaborarea manualului de prezentare.

VI.1. Transferul metodelor si experimentarea acestora la beneficiar

VI.2. Elaborarea manualului de prezentare si utilizare a metodelor de dozare a *acidului glicirizic, principiilor amare si aminoacizilor* studiat

Making plan – objectives:

Year 2005

Phase I (September - December)

The study of the documents regarding the national and European demands for the application of modern techniques (HPTLC, GC, HPLC, AAS, UV-VIS) for the control and insurance of the quality of active substances and biotechnological products, used in the therapy of nutrition diseases and dieting.

I.1. The analysis of the data about the control of compounds from the triterpenoid saponins class

I.2. The analysis of the data about the control of compounds from the bitter substances class

I.3. Documentary studies about the validation of methods according to the European Directives

I.4. Documentary studies about the preparation of vegetable bioactive products, recommended in the therapy of nutrition diseases and dieting

Year 2006

Phase II (January - June)

The elaboration and validation in agreement with the European Directives, of some methods of analysis for the quality control of compounds from the the triterpenoid saponins class and their experimentation on biotechnological products.

II.1. Experimental studies for the elaboration of methods for the quality control of compounds from the triterpenoid saponins class

II.2. Experimental studies for the validation of the elaborated methods

II.3. Experimental studies for the validation of the methods for biotechnological products

II.4. Obtaining experimental samples of *Glycyrrhizae glabra*

II.5. The application of the elaborated methods for the determination of the triterpenoid saponins from the experimental samples obtained from the *Glycyrrhizae glabra*

Phase III (July - December)

The elaboration and validation in agreement with the European Directives, of some methods of analysis for the quality control of compounds from the bitter substances class and their experimentation on biotechnological products.

III.1. Experimental studies for the elaboration of methods for the quality control of compounds from the bitter substances class

III.2. Experimental studies for the validation of the elaborated methods

III.3. Obtaining experimental samples of *Taraxacum officinale*

III.4. The application of the elaborated methods for the dosing of bitter substances from the experimental samples obtained from the *Taraxacum officinale*

Year 2007

Phase IV (January – June)

The elaboration and validation in agreement with the European Directives , of some methods of analysis for the quality control of compounds from the amino-acids class and their experimentation on biotechnological products.

IV.1. Experimental studies for the elaboration of methods for the quality control of compounds from the amino-acids class

IV.2. Experimental studies for the validation of the elaborated methods

IV.3. Experimental studies for the validation of the methods for biotechnological products

IV.4. Obtaining experimental samples of *Phaseolus vulgaris*

IV.5. The application of the elaborated methods for the determination of amino-acids from the experimental samples obtained from the *Phaseolus vulgaris*

IV.6. The dissemination of information through information and publication

IV.7. The dissemination of information through information and publication

Phase V (July - December)

The elaboration of standards (quality specifications) in agreement with the European Reglementation

V.1. The elaboration of specification of quality for bioactive products with glycyrrhizinic acid

V.2. The elaboration of specification of quality for bioactive products with bitter substances

V.3. The elaboration of specification of quality for bioactive products with amino-acids

V.4. The elaboration of scientific papers

Year 2008

Phase VI (January - June)

Technological transfer and the elaboration of the presentation manual.

VI.1. The transfer of the methods and their experimentation to the beneficiary

VI.2. The elaboration of the presentation manual and the use of the determination methods of the glycyrrhizinic acid, bitter substances and amino-acids that were studied.

Rezultate pe etape:

Etapa I

- S-a realizat un studiu documentar privind controlul unor compusi din clasa saponine triterpenice din *Glycyrrhizae glabra* si principii amare din *Taraxacum officinale*.
- S-a efectuat un studiu privind criteriile generale de validare a acestor metode de analiza conform cerintelor Directivelor Europene .
- S-a realizat un studiu documentar referitor la obtinerea unor preparate bioactive recomandate in terapia bolilor de nutritie si dieta .

Etapa II

- S-a elaborat o metoda HPLC care asigura analiza simultana a saponinei triterpenice (glicirizina sau acidul glicirizic) si agliconului ei (acidul gliciretic), obiectiv dificil de realizat deoarece acesti compusi au proprietati fizico-chimice diferite (acidul gliciretic fiind lipofilic iar acidul glicirizic puternic hidrofilic).
- S-a elaborat o metoda HPTLC si s-au aplicat fie pentru evaluarea simultana a glicirizinei si a acidului gliciretic, fie pentru dozarea agliconului si conversia sa in saponina triterpenica respectiva.
- S-au efectuat studii experimentale privind validarea metodelor elaborate pentru acidul gliciretic, urmarindu-se urmatorii parametri: liniaritatea, specificitatea, precizia, limita de cuantificare si limita de detectie.
- S-a efectuat un studiu de validare prospectiva pentru metodele de obtinere ale produselor biotehnologice cu cel mai mare continut in acid glicirizinic.
- S-au elaborat studii biotehnologice si s-au dezvoltat metode pentru obtinerea unor extracte totale si fractuni imbogatite in saponine sau agliconi triterpenici din radacinile speciei *Glycyrrhizae glabra*.
- S-au elaborat studii farmaceutice si s-au dezvoltat metode pentru conditionarea extractelor totale si fractiunilor imbogatite in agliconi triterpenici sub doua forme farmaceutice: solutie pentru administrare interna si capsule.
- S-au obtinut produse originale noi obtinute din compusi fitochimici izolati din *Glycyrrhizae glabra*
- S-au aplicat metode de cromatografie de lichide de inalta performanta, HPLC si HPTLC stabilite si s-au optimizat pentru a permite evaluarea saponinei triterpenice principale, glicirizina, din materii prime (extracte totale si fractiuni imbogatite in principii active) si produse conditionate (solutii buvabile si capsule) obtinute din *Glycyrrhiza glabra*.

Etapa III

- S-au experimentat patru procedee pentru evaluarea principiilor amare : o metoda HPTLC pentru identificarea lactonelor sesquiterpenice, o metoda HPTLC cuplata cu HPLC pentru obtinerea profilului cromatografic, o metoda HPLC pentru lactone terpenice si o alta metoda pentru evaluarea globala a principiilor amare.
- S-au elaborat doua metode HPLC pentru evaluarea unor compusi flavonoidici.
- S-au validat metodele elaborate, pentru dozarea luteolinului si apigeninei si s-au studiat, conform legislatiei internationale, urmatorii parametri de performanta analitica: liniaritatea, specificitatea, precizia, limita de cuantificare si limita de detectie.
- S-au elaborat studii biotehnologice si s-au dezvoltat metode pentru obtinerea unor produse bioactive care contin principii active totale si fractiuni imbogatite in principii amare din *Taraxacum officinale*.
- S-au elaborat studii farmaceutice si s-au dezvoltat metode pentru conditionarea produselor bioactive sub doua forme farmaceutice: comprimate si capsule.
- S-au obtinut produse originale noi obtinute din compusi fitochimici izolati din *Taraxacum officinale*.
- S-au experimentat metodele de analiza stabilite anterior si s-au optimizat pentru a permite evaluarea unor principii amare si a unor flavonoide din materii prime produse bioactive care contin principii active totale si fractiuni imbogatite in principii active amare, si produse conditionate.
- S-au studiat, dintre materiile prime, trei probe care contin principii active totale si doua fractiuni imbogatite in principii active amare.

Etapa IV

- S-a elaborat o metoda HPLC cu gradient pentru debit, pentru evaluarea aminoacizilor de interes (metionina, tirozina, fenilalanina, triptofan) prezenti in *Phaseolus vulgaris*
- S-au elaborat doua metode HPTLC, bazate pe mecanisme diferite de cromatografiere, care asigura o buna rezolutie. In functie de structura chimica a aminoacizilor de interes si complexitatea matricei se poate selecta si optimiza oricare dintre ele.
- Sa efectuat un studiu de validare al metodelor elaborate
- S-a efectuat un studiu de validare prospectiva pentru metodele de obtinere ale produselor biotehnologice cu cel mai mare continut in aminoacizii majoritari, tirozina si fenilalanina. In urma studiului de validare s-a constatat ca metoda elaborata asigura reproductibilitatea seriilor de fabricatie si produse corespunzatoare din punct de vedere calitativ.
- S-au elaborat studii biotehnologice si s-au dezvoltat metode pentru obtinerea unor produse proteice din specia *Phaseolus vulgaris* si hidroliza acestora pentru analiza aminoacizilor.

- S-au elaborat studii farmaceutice si s-au dezvoltat metode conditionarea produselor proteice sub forma de capsule gelatinoase tari cu pellete, care maresc biodisponibilitatea produsului proteic. Tehnologia de realizare permite o mai buna standardizare a produsului proteic din *Phaseolus vulgaris* in conditii industriale.
- S-au obtinut produse originale noi obtinute din compusi fitochimici izolati din *Phaseolus vulgaris*.
- S-au stabilit doua metode analitice prin aplicarea tehnicii cromatografice de inalta performanta si s-au optimizat pentru a permite evaluarea *aminoacizilor*, din materii prime (produse proteice) si produse conditionate obtinute din *Phaseolus vulgaris*.
- Sau elaborat trei lucrari stiintifice (una pentru publicare)
- S-a participat la doua evenimente stiintifice

Etapa V

- S-a elaborat Specificatia de calitate pentru dozarea acidului glicirizic din produse biotehnologice (extract total si fractiuni imbogatite in saponine triterpenice) obtinute din *Glycyrrhiza glabra*.
- S-a elaborat Specificatia de calitate pentru dozarea acidului glicirizic din produse conditionate sub forma de solutie buvabila si capsule gelatinoase tari obtinute din *Glycyrrhiza glabra*.
- S-a elaborat Specificatia de calitate pentru dozarea aminoacizilor majoritari din produsul proteic obtinut din *Phaseolus vulgare*.
- S-a elaborat Specificatia de calitate pentru dozarea principiilor amare din produse bioactive care contin principii amare (extract total) si fractiuni imbogatite in principii amare , precum si produse conditionate sub forma de capsule gelatinoase tari obtinute din *Taraxacum officinale*.
- S-a elaborat Specificatia de calitate pentru dozarea aminoacizilor majoritari din produsul conditionat sub forma de capsule gelatinoase cu pellete obtinut din *Phaseolus vulgare*.
- Sau elaborat trei lucrari stiintifice (una pentru publicare)

Etapa VI

- S-au transferat catre Departamentul Productie al INCDCF-ICCF noile metode biotehnologice, farmacologice si analitice elaborate conform Directivelor Europene, pentru controlul si asigurarea calitatii unor substante din clasa saponinelor triterpenice, a principiilor amare si respectiv din clasa aminoacizilor.
- S-au experimentat metodele pe sarje zero obtinute de Departamentul Productie, pentru patru produse biotehnologice bioactive :
 - produs biotehnologic bioactiv obtinut din *Glycyrrhiza glabra* (fractiune imbogatita in saponine triterpenice) ;
 - produs biotehnologic bioactiv obtinut din *Glycyrrhiza glabra* (extract total) ;
 - produs biotehnologic bioactiv obtinut din *Taraxacum officinale* (fractiune imbogatita in principii amare) ;
 - produs proteic obtinut din *Phaseolus vulgaris* (fractiune imbogatita in aminoacizi).
- S-au intocmit Procesul verbal de transfer a metodelor elaborate si Raportul de transfer tehnologic si experimentare.
- S-a redactat Manualul de prezentare si utilizare a metodelor, care cuprinde:
 - Procedura de operare specifica, ICCF-POS-207 pentru " Determinarea continutului - substanta activa- prin metoda HPLC"
 - Specificatie de calitate pentru dozarea acidului glicirizic
 - Specificatie de calitate pentru dozarea principiilor amare
 - Specificatie de calitate pentru dozarea unor aminoacizi
- Se constata din materialele intocmite ca metodele elaborate :
 - indeplinesc criteriile de performanta prevazute de Directivele Europene pentru standardizarea unei metode de analiza;
 - se pot aplica unei game variate de produse biotehnologice bioactive si forme de conditionare.

Results in stages:

Phase I

- It was realised a documentary study regarding the control of some compounds from triterpenoid saponins class at *Glycyrrhizae glabra* and bitter substances class from *Taraxacum officinale*.
- It was effectuated a study about the general validation criteria of these analytical methods according to the European Directives demands.
- It was realised a documentary study about the obtaining of bioactive preparations, recommended in the therapy of nutrition diseases and dieting.

Phase II

- It was elaborated a HPLC method which ensures the simultaneous analysis of the triterpenoid saponin (glycyrrhizin and glycyrrhizinic acid) and her aglicon (glycyrrhetic acid); it was a difficult goal to achieve because

these compounds have different physical-chemical properties (glycyrrhetic acid is lipophilic and glycyrrhizic acid is strong hydrophilic).

- It was elaborated a HPTLC method and was applied for the simultaneous evaluation of glycyrrhizin and glycyrrhetic acid, or for the dosage of aglicon and her conversion in their triterpenoid saponin.
- They were effectuated experimental studies about the validation elaborated methods for the glycyrrhetic acid, aiming the following parameters: linearity, specificity, precision, limit of quantification and detection limit.
- It was effectuated a prospective validation study for obtaining methods of the bioactive products with highest content in glycyrrhizic acid.
- They were elaborated biotechnological studies and were developed the obtaining methods for some total extracts and fractions enriched in triterpenoid saponins and aglicons of *Glycyrrhizae glabra* roots species.
- They were elaborated pharmaceutical studies and were developed conditioning methods for a total extracts and fractions enriched in triterpenoid aglicons in the two pharmaceutical forms: internal administration solution and capsules.
- They were obtained original new products from phytochemical compounds isolated from *Glycyrrhizae glabra*
- They were applied the high performance liquid chromatographical methods, HPLC and HPTLC which have been established and were optimized for permitted the evaluation of the main triterpenoid saponin, glycyrrhizin, from the raw materials (total extracts and fractions enriched in active principles) and conditioned products (buvabile solutions and capsules) obtained from *Glycyrrhiza glabra*.

Phase III

- They were experienced four processes for evaluation of bitter principles: one HPTLC method for the sesquiterpenoid lactone identification, one HPTLC method coupled with HPLC for the chromatographic profile obtaining, one HPLC method for the triterpenoid lactones and an another method for global evaluation of bitter principles.
- They were elaborated two HPLC methods for evaluation of some flavonoidic compounds.
- They were validated elaborated methods, for the dosage of luteoline and apigenine and they were studied, according to international law, the following parameters of analytical performance: linearity, specificity, precision, limit of quantification and detection limit.
- They were made biotechnological studies and it was developed a method for the obtaining of some bioactive products which contain active total principles and fractions enriched in bitter principles from *Taraxacum officinale*.
- They were made pharmaceutical studies and they were developed methods for the bioactive products conditioning in two pharmaceutical forms: tablets and capsules.
- They were obtained some original new products from phytochemical compounds isolated from *Taraxacum officinale*.
- They were tested methods of analysis set out above and it was optimized for permitted evaluation of some bitter principles and some flavonoids of bioactive raw materials which containing active principles total and enriched fractions in bitter principles and conditioned.
- It was made a study of three samples containing active principles total and two fractions enriched in bitter active principles, among raw materials.

Phase IV

- It was elaborated one HPLC gradient flow method, for amino acids of interest evaluation (methionine, tirosine, phenylalanine, tryptophan) present in *Phaseolus vulgaris*.
- They were elaborated two HPTLC methods, based on different mechanisms of chromatography, which ensure a good resolution. Depending on the amino acids interest chemical structure and the complexity of matrix can select and optimize any of them.
- It was effectuated a validation study of methods developed.
- It was effectuated a prospective validation study of obtaining methods of biotechnological products with highest major amino acids content in, tirosine and phenylalanine. It was found, on basis, of the validation study that the method developed ensures reproducibility of the manufacturing series and the qualitatively corresponding products.
- They were elaborated biotechnological studies and it was developed obtaining methods for some protein products of *Phaseolus vulgaris* and their hydrolysis for amino acid analysis.
- They were elaborated pharmaceutical studies and it was developed conditioning methods for the protein products in hard gelatinous capsules with pellets, which increases the bioavailability of proteic product. The realization technology allow a better standardization under industrial conditions of a proteic product from *Phaseolus vulgaris*.
- It was obtained some original new products from phytochemical compounds isolated from *Phaseolus vulgaris*.

- They were established two analytical methods by applying the high performance liquid chromatographic technique and it was optimized for permitted evaluation of some amino acids, of raw materials (protein products) and conditioned products from *Phaseolus vulgaris*.
- It was developed three scientific works (one for publication)
- It was participated in two scientific events .

Phase V

- It was elaborated The Quality Specification for the determination of glycyrrhizinic acid from biotechnological product (total extract and fractions enriched in triterpenoid saponins) obtained from *Glycyrrhiza glabra*.
- It was elaborated The Quality Specification for the determination of glycyrrhizinic acid from conditioned products in buvable solution and gelatinous capsules forms obtaining from *Glycyrrhiza glabra* .
- It was elaborated The Quality Specification for the determination of major amino acids from protein product obtaining from *Phaseolus vulgaris*.
- It was elaborated The Quality Specification for the determination of bitter principles of bioactive products (total extract) and enriched fractions in bitter principles and conditioned products in gelatinous capsules forms obtained from *Taraxacum officinale*.
- It was elaborated The Quality Specification for the determination of major amino acids from the conditioning product in gelatinous capsules with pellets form obtaining from *Phaseolus vulgaris*.
- It was developed three scientific works (one for publication)

Phase VI

- According to European Directives it was transferred to Production Department of INCDCF-ICCF The new biotechnological, pharmacological and analytical elaborate methods, for the control and quality assurance of some substances from triterpenoid saponin class, bitter principles class and amino acids class.
- They were tested these methods on zero charge obtained in the Production Department, for four biotechnological bioactive products:
 - biotechnological bioactive product obtained from *Glycyrrhiza glabra* (fractions enriched in triterpenoid saponins) ;
 - biotechnological bioactive product obtained from *Glycyrrhiza glabra* (total extract) ;
 - biotechnological bioactive product obtained from *Taraxacum officinale* (fractions enriched in bitter principles) ;
 - protein product obtained from *Phaseolus vulgaris* (fractions enriched in amino acids).
- I was worked out The Minutes of the Transfer of Methods Developed and The Report of Technology Transfer and Testing.
- It was drafted The Manual of Presentation and Use of Methods, comprising:
 - The Operating Specifical Procedure, ICCF-POS-207 from " The determining of content - the active substance-HPLC method "
 - The Quality Specification for glycyrrhizinic acid dosage
 - The Quality Specification for bitter principles dosage
 - The Quality Specification for some amino acids dosage
- It is found from the drawn materials that the developed methods :
 - meet the performance criteria stipulated by European Directives for the standardization of an analytical method;
 - may apply them at a wide range of biotechnological bioactive products and conditioning forms.

Elaborarea de lucrari stiintifice:

1. **“Studii privind obtinerea si caracterizarea unor preparate farmaceutice cu Glycyrrhiza Glabra L”;**
Autori:Nita S, Colceru-Mihul S, Andries A, Moscovici M, Rughinis D, Paraschiv I, Bazdoaca C, Andries C;
 Congresul National de Farmacie Ed.aXIII-a / Cluj-Napoca / sept.2006;
2. **“Studii privind obtinerea si caracterizarea produselor farmaceutice de origine vegetala folosite in terapia bolilor de nutritie si dieta”;**
Autori: Nita S, Moscovici M, Colceru-Mihul S, Rughinis D, Paraschiv I, Vintila M, Bazdoaca C, Vamanu A, Andries A, Hancu L;
 Al IV-lea Simpozion cu participare internationala INCDCF-ICCF Bucuresti “Cercetarea medicamentului intre informatie si stiintele vietii” / Bucuresti / oct.2006
3. **“Studii privind obtinerea si caracterizarea unor extracte si forme farmaceutice recomandate in terapia bolilor de nutritie si dieta” ;**
Autori: Adrian Andries, Sultana Nita, Adrian Vamanu, Ileana Paraschiv, Domnica Rughinis, Svetlana Colceru-

Mihul, Mihaela Vintila;
'Revista de Chimie' (sub tipar)

Participarea la manifestari stiintifice:

- Congresul National de Farmacie, Editia a XIII-a, septembrie 2006 Cluj-Napoca ;
- Al IV-lea Simpozion cu participare internationala, INCDCF - ICCF, octombrie 2006 Bucuresti.