



The State Institute for Drug Control

Slovak Republic

ANNUAL
REPORT

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Preface

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Dear ladies and gentlemen,

I have the pleasure of presenting you the Annual Report 2006 of the State Institute for Drug Control.

Presently there have been on-going reforms in the health service in the Slovak Republic. The key target is to reinforce the responsibility of citizens as well as the state institutions responsible for the realisation phase of the general health policy. The mission of SIDC in the health care system is executing of the state administration in the field of human pharmacy and drug precursors. SIDC is a budget organization directly governed by the Ministry of Health of the Slovak Republic and its task resulting from the act on medicinal products and medical devices is ensuring the state supervision and performing inspections of all pharmaceutical

activities on the area of good manufacturing practice, good distributing practice, good laboratory practice, good clinical practice and good pharmacy practice in SR. To the main tasks of SIDC belong also the supervision over the quality, safety and efficacy, decisions making on registrations of human medicines, issuing licences for activities with specified substances, registration of medical devices, as well as the other activities following the current legislation.

Recently SIDC has passed through a long way of approximation of the national legislation with EU legislation related to the pharmaceutical testing, pharmacologically-toxicological testing, clinical trials of medicines, manufacture and dispensing of medicinal products, package labelling, information duties and advertisement of medicinal products.

From the view of membership of SR in European Union one of our priorities is the cooperation with the European organisations and institutions in the framework of Council of Europe, cooperation with the European Medicines Agency, European Pharmacopoeia Committee, European Commission, OMCL network, OECD in the field of Good Laboratory Practice and other medicines agencies of EU member states. In the worldwide context SIDC collaborates with WHO and PIC/S scheme, too.

In the next period the ambition of SIDC is to increase the transparency towards all of the participants in the medicines chain - i.e. towards the manufacturer, distributor, pharmacist, physician, professional physician associations, as well as the patient himself and the patient organisations.

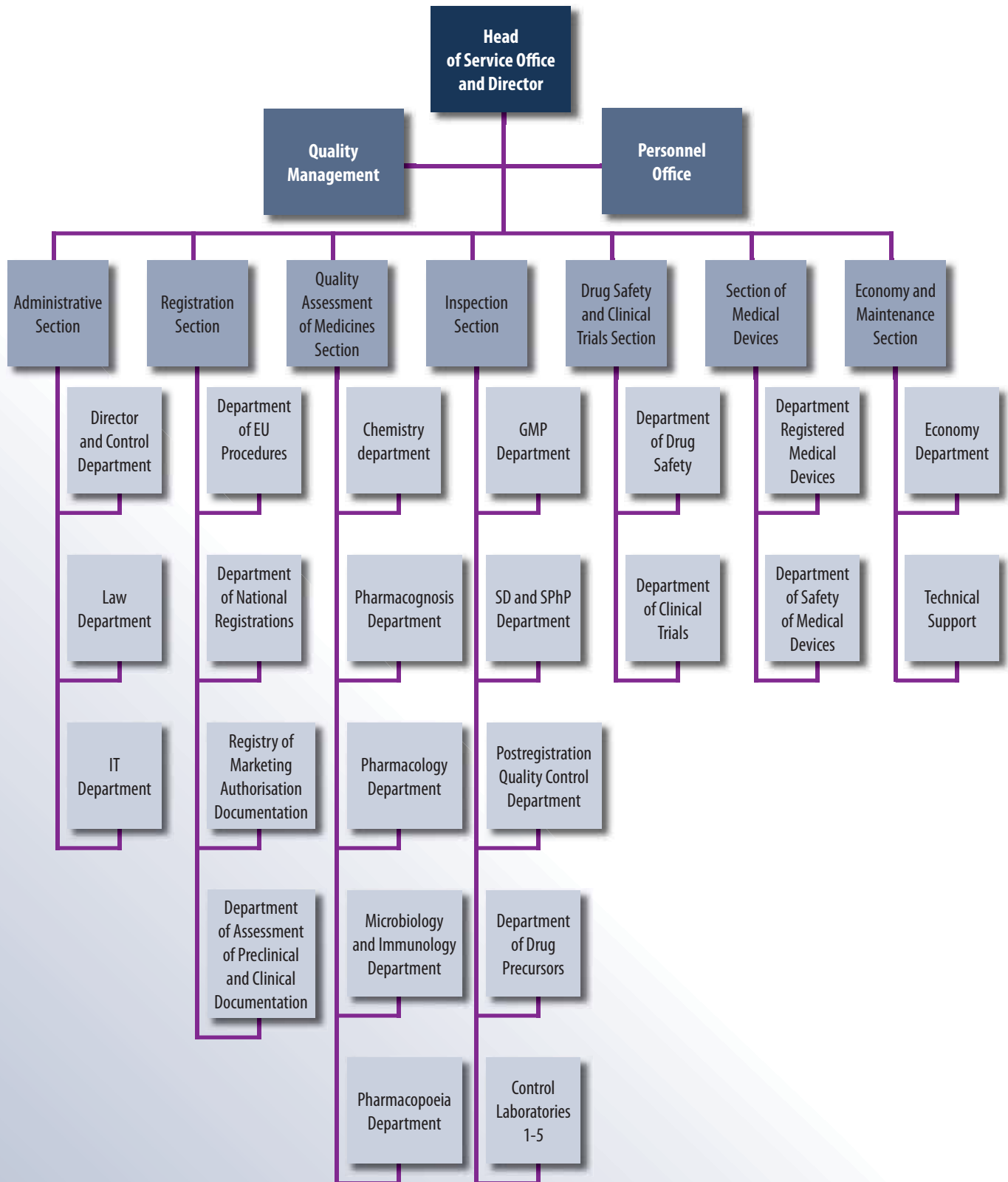
I'm convinced that the steps we take in this area will bring in the near future the new extent in the awareness about medicines and medical devices registered in the SR and about the procedures performed by the SIDC in the framework of ensuring the state supervision and inspection of providing the health care.

Finally I would like to thank to all SIDC staff whose daily work ensured the patients to have the good quality, safe and effective medicines.

PharmDr. Ján Mazag
Head of Service Office and Director



Organizational Structure State Institute for Drug Control



About SIDC
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The State Institute for Drug Control is according to the article 58 of the Act No. 140/1998 Coll. on medicinal products and medical devices, on the amendment of the Act No. 455/1991 Coll. on small trade business (Small Trade Business Act) as amended, and on the amendment and supplement of the Act of the National Council SR No. 220/1996 Coll. on advertising as amended, the authority of the state administration in the field of human pharmacy and drug precursors.

SIDC is a state budget organization directly governed by the Ministry of Health of the Slovak Republic. At the head of SIDC is a Head of Service Office and Director, appointed and recalled by the Minister of Health of SR.

SIDC is an organization that ensures the state supervision and performs inspection of all pharmaceutical activities in the area of Good Manufacturing Practice, Good Distributing Practice, Good Laboratory Practice, Good Clinical and Good Pharmacy Practice in SR. The supervision over the quality, safety and efficacy, decisions making on registration of human medicines and registration of medical devices with the statement of compliance, registration of medical devices on the basis of CE certificates of the notified persons EU, as well as the other activities following the current legislation is being a part of it.

1. The mission and perspective of SIDC
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SIDC mission is ensuring and control of the quality, efficacy and safety of medicinal products and medical devices, issuing the decisions on the registration of human medicines, performing the state supervision in the field of human pharmacy, executing of state administration in the matters of drug precursors, the control of manufacture and wholesale distribution of medicinal products and medical devices as well as the cooperation with the EU organisations.

In addition to above mentioned activities SIDC carries out inspections of compliance with the principles of Good Manufacturing Practice, Good Clinical Practice, Good Laboratory Practice, Good Distributing Practice and Good Pharmacy Practice and the observance of provisions of the Slovak Pharmacopoeia and the Slovak Pharmaceutical Codex in the process of preparation mass and individually prepared medicines. Furthermore, SIDC compiles the Slovak Pharmacopoeia and the Slovak Pharmaceutical Codex (art. 45), keeps the database of registered medicinal products and medical devices and according to the Act No140/1998 Coll. imposes fines for shortcomings being disclosed.

International cooperation is focused on the activities resulting from the membership of SR in EU as well as on the development of the cooperation and exchange of information with the member states of OECD.

Another important activity is the cooperation with the European Directorate for the Quality of Medicines in the view of the unified implementation of the quality system in laboratories in the framework of the mutual recognition of results, as well as the cooperation and the participation in the periodical sessions of EMEA.

No less important part is the Good Laboratory Practice, where the SIDC employee represents SR in the Working Group for GLP in the framework of OECD and in the Working Group in EC.

Within the international cooperation the special importance has the representation of SIDC and SR by the expert lectures in the various international and domestic conferences,



seminars and workshops, which are performed by the expert employees of SIDC.

In the framework of the mission and perspective of SIDC was elaborated the legislative intent of Agency for Human Pharmacy which was appointed to the proceedings of government SR. In this material SIDC was defined as the central agency of state administration in the matters of human pharmacy and drug precursors.

Present government violated the Government Decree No 644 of 7th September 2005 on the legislative intent of Agency for Human Pharmacy due to its non-compliance with the Statement of policy of the government SR. The government recommended keeping the existing legal form in the matters of human pharmacy and drug precursors.

2. Activities of SIDC

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2.1 Quality Management

The international cooperation has been developed on the basis of collaboration and exchange of information between the member states of OECD according to the plan. The survey and assessment of the inspection activity „Annual Overview of GLP in the Slovak Republic 2006“ has been elaborated and submitted to the Environment Directorate OECD, European Commission and consequently to the all member states according to the directions.

In the framework of benchmarking continued the international cooperation with EMEA by the preparation of evaluation of the quality systems implementation – audits of particular agencies. On the basis of requirement of EMEA was elaborated document „Template Benchmarking“ and questionnaire on the procedure and programme of monitoring SR in the field of drug GLP.

Scheduled BEMA visit from European Medicines Agency EMEA – the assessment of implementation of quality system according to ISO 9004, ISO 19011 extended by specific chapters PERF III - was performed in April 2006. It was evaluated the complex quality system according to the international norms. According to the report of BEMA visit were by analysis identified non-compliances and it was elaborated summary – schedule of corrective actions. The corrective actions were monitored. Some findings or recommendations of inspectors were dissolved immediately without the need of financial provision, but another of them require longer time slot with ensuring of financial provisions as well as expert employees.

Within the international cooperation SIDC actively participated in the Twinning project with Turkey via ÚNMS (Office for Standards, Metrology and Testing) and was approved by EC as „Mandate Body“ for Twinning project in the field of GLP and Twinning project in the field of Medical Devices. Two-year „Twinning project GLP Turkey“ is financed and approved by EC. In the frame of project details for working plans of training were elaborated, complex materials were prepared and expert consultancy and lector activity was performed.

Assurance of quality system SIDC

Implementation of the quality system according to STN EN ISO 9000:2000 and STN EN ISO/17025 in laboratories proceeded. Internal directives were updated according to topicality.

Survey of issued (new, updated) controlled documents in 2006 and their total number

Summary of the issued controlled documents is presented in the table

Document	Issued in 2005	Total number
Quality Manuals	1	8
Internal Directives (ID)	6	33
Guidelines	4	24
Internal Guidelines (ID)	2	12
Standard Operating Procedures (SOPs)	42	720

During the year were performed 4 sessions of Quality Managers, where the procedure and implementation of quality systems have been discussed. Quality managers gave accounts on every audit of quality management department performed according to the plan.

From the comparison of evaluation results, that the activity level of QM in 2006 was moderately decreased compared to the last year. Decrease of activity was caused by many personal and space changes (moving to the new place, redeployment within the institute for another activities, in which the employees have to be adapted at first, retirement of employees and onset of new ones, external controls on the part of state authorities).

By the reason of the permanent personal changes the internal audits were not performed according to the plan. Another reason was extraordinary external controls on the part of governing bodies and subsequent internal controls focused on the fulfilment of corrective actions.

Internal audit was performed only at the Medical Devices Section after the stabilization of personal and space changes. Internal audits at the other sections will be performed gradually in 2007.

In the framework of supervision of laboratories which have the permission to perform pharmaceutical testing and pharmacologically-toxicological testing the inspections were performed according to the plan.

At present 9 laboratories are registered with permission to perform pharmaceutical and pharmacologically-toxicological testing. Their survey has been regularly updated and had been published on the SIDC website and in the magazine „Lekárnik“.

2.2 Administrative Affairs

Control department

On the basis of the plan of control activity these control actions were performed these internal controls:

- control of observance of the Act No. 330/2006 Coll. as amended by the Act No. 158/2001 Coll. on the work safety and health protection
- control of observance of the Act No. 314/2001 Coll. on fire protection
- control of observance of the Act No. 42/1994 Coll. on civil deference as amended
- control of observance of provision 29 art.3 of the Act No. 431/2002 Coll. on accounting concerning the financial resources, as well as the control of handling with valuables
- control of observance of the Act No. 81/2005 Coll. in term of later provisions on travelling expenses



- control of utilization of common expenses
- control of utilization of capital expenses
- control of amount outstanding

Handling of petitions and complaints

In 2006 were at central registration of petitions and complaints registered 18 administrations the content of which was qualified as complaint and thus they were subject to proceeding in term of Act No. 152/1998 Coll. on complaints.

In the case of justified complaint there were taken corrective measures. In 3 cases have started administrative proceeding and the penalty was imposed. On the basis of requirement of MH SR was submitted "Information on handling petitions and complaints in 2006".

Public Relations & Communication

PR & Communication Division ensured the performing of tasks resulting from the position of division as the press office of the Head of Service Office and Director and continuously performed the monitoring of media. PR & Communication division coordinated the communication of SIDC with media. There were executed 135 applications received from print and electronical media.

In cooperation with others SIDC sections the PR Division has participated in realization of Annual Report, at the same time coordinated activities related to translation and ensured works related to the publishing of English version of Annual Report. PR & Communication division in cooperation with IT department regularly updated SIDC internet and intranet websites on the basis of requirements of expert sections.

PR & Communication Division coordinated cooperation between SIDC and external companies in the development of the new website, which should be put into operation in February 2007. Similarly PR Division cooperated in the development of new logo of SIDC and in elaboration of Design Manual of SIDC.

PR & Communication Division has kept the evidence and handled agenda concerning all of the applications submitted to SIDC in the terms of the Act No. 211/2000 Coll. on the free access to information. Totally 253 applications for information were received and executed.

Overview of the submitted applications for information

Public Relations dept. has been established since the 1st July 2003. PR provides statements for media, monitors the press information and executes the agenda accordint the Act of the free access to information No 211/2000 (has come in force since 1st January 2001).

	2001	2002	2003	2004	2005	2006
Number of the submitted applications for information	27	19	53	206	216	253
Number of provided information	27	19	52	204	215	253
Appeal for completion of the application	-	-	-	1	-	-
Issue of the decision about non-providing of information	-	-	1	1	1	-

Overview of the media communication

	2004	2005	2006
Print Media	67	64	88
TV	15	14	25
Radio	3	3	8
Press Agency	1	3	8
Internet Portal	1	-	6
Press Conference	-	2	-
Totally	87	86	135

EU Collaboration

International cooperation was focused on the activities resulting from the membership of the Slovak Republic in the EU, on the strengthening of cooperation and exchange of information.

Furthermore, an important issues was the cooperation with the Council of Europe, i.e. EDQM and OMCL, in purpose of the unified implementation of the quality system in laboratories in the framework of the mutual recognition of the results.

Nominated representatives of the Slovak Republic actively participated in the regular sessions of working groups and committees of PIC/S, EMEA, OECD and European Commission.

Metrology

Quality of measuring instruments and measuring equipments being in use in the Quality Assessment of Medicines Section has been ensured in particular in compliance with the requirements of Act No. 142/2000 Coll. as amended and with other related legislative standards of the Slovak Republic in the field of metrology as well as in compliance with the STN ISO standards for the demonstration of quality system operation in this area.

There were prepared and revised following controlled documents: ID 36/2006 System of control of measuring instruments, SOP Evidence of measuring instruments and related records and SOP Qualification of analytical equipment. Revision of the other controlled documents is in-process.

On deputy of the Quality Assurance Management the external audit as supervision was performed in the Testing laboratory Bratislava Bell/Novamann, International, Ltd.

On the request of the Inspection Section the metrologist participated in 2 GMP inspections.

On the basis of agreement between SIDC and SNAS two GLP inspections were performed.

At the Informatics department – Administrative Affairs Section three internal audits of second level were performed according to STN EN ISO 9001.

Metrologist of the Institute regularly participated in the session of the Commission for certified reference materials, which is the advisory body of director of the Slovak Metrological Institute.

In the framework of cooperation agreement between ÚNMS SR (Office for Standards, Metrology and Testing) and SIDC the metrologist of Institute participated in „Twinning Project TR/2004/IB/EC/06, Strengthening the ministries of health, environment and forests, and agriculture and rural affairs to harmonize and implement legislation in the field of Good Laboratory Practice for non-clinical health and environmental protection“ for Turkey.



Informatics

In terms of electronic processing of the registration documentation the IT department closely cooperated with the Registration Section. The department made out the identification lists, assigned SIDC codes for the medicinal products registered by the national and European procedures, updated the database of registered medicinal products by filling up the card of decision and the card of medicinal product by necessary data.

The database of companies and database of ATC groups was updated according to the WHO data.

Department employees participated at common working meetings of the company MCR and Registration Section concerning the further development of information system of medicinal products and continuously performed advisory and consultant activity for the employees of the Registration Section.

The employee of department proceeded in continuous processing of the approved package leaflets and SPC supplied by manufacturers and in scanning of working documentation (electronical archive of department).

Department has continuously performed works related to the maintenance and updating of SIDC website, with receiving, classifying and sending of electronical post. The cooperation between SIDC and authors of AISLP proceeds in the form of the mutual exchange of data.

On the basis of contract between SIDC and authors of programme NOBEL is performed regular supplying of required data from the information system of medicinal products and there are solved the remarks supplied by the authors of programme NOBEL.

The department ensured operating and service of computer technology and photocopying machine of SIDC. The department cooperated with the management within the purchase of computer technology and expendable supplies and provided expert help to the users of IT in the work with installed programmes. Technicians, programmers of SIDC worked on the development of simple programmes for internal use of the institute.

It was realized the competitive bidding for purchase of electronical registry. The winner of competition became the company DATALAN. The department ensured the training of the staff.

Law Affairs

At the division for administrative proceedings was registered totally 62 cases. From the mentioned number was in terms of the art.18 of the Act No. 71/1967 Coll. on administrative proceedings in the full version started administrative proceeding in 41 cases and in the terms of art.46 of the act on administrative proceedings were issued totally 34 decisions imposing fines to physical persons and legal persons in the sum 715 000 SKK.

In connection with the medicinal products EUKLAZID and DIAPREL, previously prosecuted by Registration Section, was by the division for administrative proceedings processed 8 decisions in the terms of art.46 of the act of administrative proceedings. The proceeding started at the instance of the participants of administrative proceeding and the supervision in the administrative proceeding was executed by the procurator of the Attorney Generalship of SR. All decisions came into force because the procurator didn't recall the decisions within the supervision and the participants of proceeding didn't appeal against the decisions.

The division for the supervision of the medicines advertisement registered 323 notification of medicines advertisement according to the Act No. 140/1998 Coll. on medicinal products and medical devices and the Act No. 147/2001 Coll. on advertisement as amended.

Moreover according to art.11 of the act on advertisement there were issued 4 decisions on prohibition of advertisement distributing, in 3 cases the administrative proceeding was

stopped and it was approved 1 conciliation. At the same time the fines were imposed in the total sum 320 000 SKK.

In addition to this activity the information was provided according to the Act No. 211/2000 Coll. on free access to information and on amendment and supplement of some acts and legal advices were provided to the physical and legal persons.

At the same time the legal aid was provided the Registration Section concerning the implementation of the EU legislation.

2.3 Registration of Medicines

Activities of the Registration Unit in 2006 focused mainly on:

- strengthening of organisation and human resources,
- implementation of requirements of the revised pharmaceutical legislation according to the Act No. 342/ 2006 Coll. ,
- finalisation of applications in backlog,
- rationalisation of procedures: new systematic planning was introduced along with better coordination of in-house expertise and cooperation,
- transparency in the work of the Committee of Drugs.

Staff members took part in the collaboration within the European Medicines Agencies Network in several committees and working parties (Coordination Group, Herbal Medicinal Product Committee, Notice to Applicants, QRD/PIM, Name review group, Homeopathic Medicinal Product Working Group, e-TIG, EWP).

We have actively participated in two WHO events: ICDRA conference in Soul and a consultation meeting on technical regulatory documentation in Genève.

3 conferences for stakeholders have been organized: update on regulatory issues, implementation of revised legislation and generic medicinal products.

Twinning Light Project „Strengthening of SIDC capacities for implementation of new EU legislation Directive 2001/83/EC and Directive 2004/27/EC“ has been approved and shall be organized in 2007.

Department of logistics (receipt and control of documentation)

Department with following responsibilities has been created:

- assignment of variable symbols for fees and check of fees
- receipt of marketing authorisation applications
- application tracking database
- check-in of documentation
- library of registration documentation and decisions
- exchange of documentation with assessors
- validation of decisions

Department of national registrations focused on:

- coordination of national registrations, variations and renewals and particularly on those in the backlog;
- SPC, PIL revision with a perspective to move to QRD;
- EU harmonisation.



Department of national registrations

Type of application	start	accepted 2006	finalised 2006	withdrawn 2006
new application	547	91	113	33
renewal	1797	503	815	32
transfer	166	130	156	1
variation	3148	964	1891	166
variation 1A	729	2118	1552	18
variation 1B	484	1370	1009	11

Department of EU procedures

Focused on:

- coordination of mutual recognition and decentralise procedures,
- revision of SPC, PIL and labelling in Slovak according to the QRD templates, including centralised procedures,
- referrals,
- active participation in drafting of regulatory guidance. in the EU.

Department of EU procedures

Type of application	accepted 2006	finalised 2006
DCP new application	301	6
MRP new application	359	430
MRP notification	2418	1863
MRP variation	708	539
MRP renewal	72	3
Transfer	25	22
Referrals	28	48
CP-QRD n		100%
COMP-QRD		100%

Department of pre-clinical and clinical assessment

The core activity of the future department has been set up:

- coordination of the work of the Committee for Drugs
- 17 new external assessors
- early identification of a potential risk to public health
- preparation for future TMS role,
- participation in EWP meetings.

Committee for Drugs

Commission started to work in a new composition and with a new Mandate and Rules of procedure. Transparency increased by regular publishing of an agenda and a press release from monthly meetings.

Committee met 10-times as planned and discussed **271** applications, from which:

- **261** applications with a positive recommendation,
- **6** applications have been postponed
- **1** application with a negative recommendation.

Subcommittee for herbal medicinal products and homeopathics met once.

2.4 Quality Assessment of Medicines

Quality Assessment of Medicines Section is an executive professional division of the SIDC. The section is divided into 5 departments:

- Pharmacopoeia department
- Pharmacology department and experimental Animal House
- Microbiology and Immunology department
- Pharmacognosis department
- Chemistry department

One of the most important points in the plan of main tasks of the section is the assessment of the quality of medicinal products in the various types of the medicines registration procedures. The result of this assessment is the elaboration of the Assessment Report on the chemical, pharmaceutical and biological part of the registration documentation.

The assessments on the quality were finished for the medicinal products Halea tbl, Belupo, Croatia and Endiex cps, Zentiva Inc., CZ, where the Slovak Republic will fulfil the task of reference member state.

In the framework of international collaboration the section as an OMCL SR participated in 3 PTS studies organized by EDQM in Strasbourg. In **PTS 083** was achieved an excellent result, z-score = 0,07 for sample B. (Laboratory results are acceptable if z-score is in interval +/- 2). The second and third studies **PTS 084 and PTS 085** are in-process.

OMCL participated in analysis of **MRP products** registered in the mutual recognition procedure. OMCL from Estonia, Finland and Ireland asked for the analysis of the medicinal product containing drugs perindopril and indapamid, at the Slovak market registered under the name NOLIPREL forte, fy Servier.

In the scheme **Collaborative studies (CS)** of the European Pharmacopoeia, which is the mean of the quality appointment (potency) and declaration of the substance as the reference material Ph.Eur., the OMCL participated in the analysis of the substance letrozole CRS 1. OMCL



achieved the excellent results. The laboratories involved in the study performed comparable values of the monitored parameters in compliance with the EDQM laboratory. Moreover our results were in accuracy 3 decimals in compliance with the OMCL from Switzerland, as one of the 6 participating OMCLs.

In the framework of EDQM programme focused on the analysis of **centrally registered medicinal products (CAP)** the OMCL performed the complete analysis of three batches of product VENTAVIS nebulizer, solution, Schering AG. The results are accepted by all of the national authorities throughout the European Union.

Employees nominated to the particular working groups of the European Commission, Council of Europe, EMEA and EDQM performed 21 business trips abroad.

In cooperation with the Slovak Medical University 16 lectures were performed by the experts of the section.

There were 15 assessments elaborated for the boundary products between the medicinal product and food supplement or cosmetics.

Pharmacopoeia department continued in the translations of the new monographs and adjustment of the modified ones of Ph.Eur. 5th edition and annexes. In 2006 were processed 1540 pages of pharmacopoeia monographs, control methods and dosage forms, which will be included in the next edition of Slovak Pharmacopoeia (SL).

The stability studies for some magistral formulas were finished. The monographs to the Slovak Pharmaceutical Codex for 60 magistral formulas passed the expert assessment and the text was subedited to the final form.

The inspection of the Animal House was carried out by the Regional Veterinary and Food Administration.

The qualifications of the new equipment for dissolution testing, UV/VIS spectrophotometer and pH metres were performed, as well as the training of operating staff.

In cooperation with company Modrá planéta were in the first half of 2006 in the terms of the Act No. 140/1998 Coll. from the external subjects collected and directly at the Pharmacognosis department destroyed 8 279 ml, 1 084 g and 24 038 piece single dosage forms containing narcotic and psychotropic substances after their expiration.

The work on the updating of the Quality manual of the section has been started.

Totally **348** samples (tab. 1) and **3 928** assessments (tab.2) were processed. 10 of the analysed samples were unacceptable from the view of average weight of tablets, packaging, assay and purity, conductivity, microbial purity and low efficacy.

The activity of section expressed financially represents **16. 302 633,-** SKK.

Tab. 1

Number of samples	Pharmacology department	Microbiology and Immunology department	Pharmacognosy department	Chemistry department
Foreign registration	-	-	-	1
Domestic registration	-	-	-	-
Obligatory control	-	-	-	11
Import	1	3	12	40
Domestic manufacture		-	-	-
Ordered	210	19	1	5
Clinical complaint	-	-	-	5
Reclamation	-	-	5	5
Internal needs (QA)	-	9	2	3
PTS/MMS/CS	-	1/0/0	-	3/0/1
Other	-	-	-	8

Tab.2

Number of Assessment Reports	Pharmacology department	Microbiology and Immunology department	Pharmacognosy department	Chemistry department
Foreign registrations	36	1	32	207
N/MRP/DCP	-	5	130	
	20		16	
Domestic registrations	-	-	-	-
Variations	362	375	766	1480
Clinical batches		-	-	-
Analytical certificates	-	284	26	33
Assessments and reviews	-	11	15	-
"Upgrade"	3	2	19	88
Other	-	17	-	-



2.5 Inspection

Range of activities:

- performing of the state supervision in the field of pharmacy,
- inspection activity,
- and control of activity of the licence holders for handling of medicinal products and medical devices according to the Act No. 140/1998 Coll. in terms of later provisions, to the Act No. 139/1998 Coll. on terms of later provisions and to the Act No. 331/2005 Coll.

National competency and competency within the cooperation in EU

- 1) performs state supervision in the field of pharmacy and drug precursors, inspection of manufacture and wholesale distribution of medicinal products and medical devices
- 2) proposes and imposes fines for shortcomings being disclosed and files a proposals for suspension or withdrawal of activity
- 3) performs inspection of compliance with the principles of Good Manufacturing Practice, Good Distribution Practice and Good Pharmacy Practice and of compliance with the provisions of the Slovak Pharmacopoeia and Slovak Pharmaceutical Codex on the process of preparation of the mass- and individually prepared medicines
- 4) issues reports, opinions and certificates on the material, space and personal equipment of the applicants for licence for handling of the human medicines and medical devices
- 5) issues permissions for handling of drug precursors
- 6) manages and regulates the activity of control laboratories
- 7) performs tasks in the field of competency in EU affairs
- 8) participates in creation and in comment proceeding of proposals of legislative provisions
- 9) within postgradual education cooperates with the Slovak Medical University
- 10) advisory and consultant activity for manufacturers, public and hospital pharmacies, dispensaries of medical devices, wholesale distribution organizations, opticians, etc.

Control laboratories 1 – 5

Control laboratories are performing the inspection activity in health facilities, control-analytical activity and other expert activity. Territorial competency of control laboratory is within the region. From the expert side the coordination proceeds with the Inspection Section SIDC Bratislava.

Inspection activity was performed:

- in the facilities providing pharmacy care (public pharmacies, branches of public pharmacies, hospital pharmacies)
- in the distribution organizations
- in another facilities (poppy producers, opticians, etc.)

Total number of inspections performed: **724**

Total number of samples taken: **254**

Overview of inspections is in Annex No. 2

Control-analytical activity was focused on:

- chemical and microbiological control of the active substances on the basis of the order for distribution organizations and hospital pharmacies (issuing of analytical certificates)
- chemical and microbiological control of medicinal preparations, purified water and packaging material on the basis of random choice
- chemical and microbiological control of purified water for pharmacies on the basis of the order

The most frequently found deficiencies:

- non-complying content of the active substance
- non-complying total amount of the sample
- non-complying conductivity of the purified water
- non-complying microbiological purity of the purified water

Another expert activity:

- consulting activity – comments on the layout of pharmacies, branches of public pharmacies, dispensaries of medical devices
- elaboration and updating of SOPs
- realization of works on the monographs for Slovak Pharmaceutical Codex
- training of employees by courses, lectures and seminars within SIDC, Slovak Medical University, Slovak Pharmaceutical Society, Slovak Society of Health Employees
- works on the stability studies of testing and volumetric solutions
- regular audits performed by Quality Managers

2.6. Drug Safety and Clinical Trials

Department of drug safety

Department of drug safety is a coordinating centre for pharmacovigilance, monitoring of adverse drug reactions in Slovak republic and surveillance of registered medicinal products for human use. Its main task is identification, monitoring, analysis, assessment and evaluation of new information on safety of drugs (so called safety signals), as well as reports of adverse drug reactions to registered medical products for human use.

In 2006 we continued to report spontaneous reports that we received from health care professionals to Eudravigilance database. We continued in development of our own national database of adverse drug reactions eSkadra for recording, archiving and transmission of reports to Eudravigilance database.



Overview of activities:

Reporting ICSR from Slovak republic (spontaneous)	873
Expedited reporting of ADR (post-registration)	40 549
Laboratory control of the batch due to ADR	12
Submitted PSURs	1049
Control of PSURs for renewal of registration	349
Published statements on drug safety	9
Reports from Slovakia submitted to Eudravigilance (year 2006)	119
Public statements issued in 2006	9
Assessment requests on OTC status	7
Assessment of type II. variations	156
Exchange of information with EU countries	
- non-urgent requests	58
- alerts	5
- other request on information	23
Drug bulletin	1
Other activities – assessment	
- Dear Doctor/Health Professional Letter	6
- „education activities“ as part of Risk mineralisation plans	2
- Methadone – core Summary of product characteristics	1

One of the tasks of department of drug safety is promotion of adverse reactions reporting. We use several means including direct posting of letters to physicians and lectures. Two issues of the bulletin "The Drug Risk" have been prepared and issued that are also available on Internet. A guideline on reporting ADR (spontaneous, solicited and from literature resources) has been issued on Internet.

The Committee on safety of drugs that is advisory body met 7 times. The Committee evaluated reported cases of adverse reactions and evaluated signals and different kind of communication.

Department of clinical trials

Department ensures processing of applications and notifications for clinical trials of investigational medicinal products, reviewing study protocols, issuing the decisions on approval of clinical trials, surveillance over its performance and approving of study centres. Tasks of department include inspection of Good Clinical Practice (GCP) as well.

We participate in the project of European database of all clinical trials in European Union–EudraCT.

Overview of the activities:

Activity	Number
Application for clinical trial	151
Authorization of clinical trials of drugs	128
Rejection of application for clinical trial	2
Application on approving of amendment to protocol	242
Application/notification on changes in Investigator's Brochure	151
Application on approving of a new study centre	19
Submission of agreement of ethical committee	135
Notice on beginning of clinical trial	38
Notice on end of clinical trial	87
Annual report on process of a clinical trial	103
Report on adverse event from Slovak trial sites	301
Notice on adverse event from abroad	5856
Own activity	69
Other	387
Application for clinical trial with medical device	3
Authorization of clinical trial with medical device	3
Inspection of GCP	8

2.7. Medical Devices

Medical Devices Section performs the duties of the competent authority for medical devices in the Slovak Republic in accordance with the Act No.140/1998 Coll. as amended and three governmental regulations No.572/2001 Coll. as amended, No.569/2001 Coll. and No.570/2001 Coll.

Medical Devices Section has 8 employees and consists of two departments, namely Department of Registered Medical Devices and Department of Safety of Medical Devices.

Department of Registered Medical Devices carries out registration of medical devices mostly on the basis of EC/CE Certificates issued by the European Notified Bodies and EC Declarations of Conformity of the Manufacturer. In 2006, the total number of new SIDC codes granted/assigned was lower due to the decrease in the number of new registrations. In most cases, Department dealt with the prolongation of validity of registration on the basis of new CE certificates, range extension of registered medical devices, change in the name of manufacturer and evidence of diagnostic medical devices in vitro.



Department of Safety of Medical Devices follows and processes notifications of manufacturers, competent EU authorities and distributors about adverse effects of medical devices. There was a significant increase of medical device accident reports from member states, alerts and newly, reports concerning the counterfeit of medical devices. Department also performed inspections of the wholesale distributing companies.

Section's two employees took part in the meetings of workgroups of the European Commission (MDEG, MSOG, NBOG, GHTF, BSE/TSE WG, EUDAMED a GMDN) and in the CA meeting in Tampere as well.

Medical Devices Section cooperates with the Ministry of Health of the Slovak Republic in the field of categorization of medical devices, i.e. introducing medical devices into the "List of medical devices fully or partially reimbursed on the basis of public health insurance". One employee attended the sessions of the Committee of the Drug Quality. Notifications concerning consumption of medical devices are also transferred quarterly to the Ministry of Health of the Slovak Republic.

Summary of activities of the Medical Devices Section:

Number of received registration forms of medical devices	1106
Notification of adverse effects of medical devices	536
New codes assigned	3093
Updated codes	4922
Inspections of wholesale distributors	16
Repeated inspections of wholesale distributors	9
Suggestions for inspections of wholesale distributors	1
Assessment reports for wholesale distribution license	11
Clinical complaints	0
Notification of clinical testing	2

3. Budget of SIDC

According to the Act on state budget for 2006 No. 655/2005 the Ministry of Health SR itemized to the Institute through the information system of exchequer to common expenses and capital expenses for the year 2006. SIDC ensured to 31.12.2006 the following utilization of the budget:

In thousands SKK *

Economic classification	Original budget to 1.1.2006	Actual budget to 31.12.2006	Utilization to 31.12.2006	% of utilization
Incomes from registration	-	-	108 901	-
Incomes from the others activities	8 000	8 000	11 445	143,06
Incomes totally	8 000	8 000	120 347	-

Common expenses	106 709	124 107	124 104	99,99
Capital expenses	48 604	25 213	22 108	87,69
Expenses totally	155 313	149 320	146 212	97,92

Incomes of the institute follow from providing services, which are chargeable. Incomes from registrations are not estimated. In comparison with the year 2005 total incomes are increased in 11 079 thousand Slovak crowns especially by the reason of increased number of registrations as well as the increase of domestic inspection activity and its extension abroad. The activity of institute in debt collection was strengthened, too.

Common expenses were utilized according to the budget, for wages and salaries in the volume 49 837 thousand SKK., for insurance and contributions to insurance companies 16 724 thousand SKK, for commodities and services 57 000 thousand SKK and for common transfers 543 thousand SKK.

Capital expenses were utilized for ensuring particular investments according to the sequential limits release from the Ministry of Health SR. Thus was ensured impletion of volumes of particular investments according to the contracts with the suppliers. Predominant volume of the capital expenses 14 114 thousand SKK was utilized for the finalization of building Extension of SIDC and for reconstruction of the Control laboratory Žilina. For purchase of machines and equipment the institute utilized the budget means in volume 7 994 thousand SKK.

* Exchange rate 1 EUR = 34 SKK



Development of selected budget indicators for the years 2004 – 2006

	2004	2005	2006
Incomes totally	107 687	109 268	120 347
Common expenses	95 438	95 438	123 561
Capital expenses	69 082	69 082	22 108

Economy and maintenance section involves also the activity Collection and disposal of waste medicines.

The collection of waste medicines took place in all public pharmacies. The pick-up and disposal of waste ensured the company Modrá planéta, Ltd. Together with the increased number of pharmacies increased also the amount of waste medicines in the year 2006 to 61 tons, which is for 16 tons more than in the 2005. Related to this activity are also the obligations of the waste holder following from the Act No.223/2001 Coll. on wastes, such as waste evidence, notifications to the Regional Office of Environment and regular updating of permissions for the handling with dangerous wastes.

4. Personnel policy

Personnel Office provided exercising all of the regulations and acts in the terms of the labour-law relations of the employees, their wage claims. The office provided keeping of records and statistics related to the above mentioned activities which are submitted to the Statistical Office of SR, the Ministry of Health and the National Centre of Health Information.

For the year 2006 were approved totally 232 berths, thereof 91 in civil service and 132 for performing works in public interest.

Number and structure of SIDC employees

Limit for SIDC employees for 2006 and filling of capacity:

Indicator	Civil service	Public service	Total
Limit for 2006	91	132	223
Reality – natural persons	83	132	215
- average re-counted status as of 31 December 2006	83	129,2	212,2
Saving (average re-counted status/limit)	8	2,7	10,7

The unfilled limit for civil servants is caused as in the last years by the protracted procedure of filling a civil servant vacancies by selection procedure, unsuccessful selection procedures, but mainly by the fluctuation of civil servants. But it should be noted, that in comparison with the year 2005 the fluctuation was partially reduced. While in 2005 it was 35%, in 2006 it was 32%.

Comparison of selected indicators from the personal work field in the last 4 years

Indicator	2003	2004	2005	2006
Average registered number of employees				
- re-counted	192,42	195,48	205,5	212,2
- in natural persons	198,00	205,00	211	215
Average month salary				
in Slovak crowns	15 677	16 177	16 412	20 500

Utilization of wage funds in 2006:

Civil service	25,838.000,- SKK
number of employees	83
average salary	26 000,- SKK
Public interest	23,999.000,- SKK
number of employees	132
average salary	15 000,- SKK

Under the present system of wage funds allocation the only way of the salary increase is not the increase of the number of employees, but obversely increase of work effectivity and rationalisation.

Selection procedures

In the year 2006 were at the SIDC performed 25 selection procedures to the 30 civil service berths. 69 participants applied to these selection procedures. From this number in the selection procedure participated 34 applicants and 23 were successful. Number of employees appointed to the civil service berths was 15. From the total number of applicants 49,2 % did not participate, 33,3% were successful.

15 of 30 berths were filled, which represents 50%. Non-participation was caused by the disestablishment of the Office for Civil Service and junction of the competencies to the particular departments.

During the realization of selection procedures all appropriate provisions of Act on civil service, regulations and service instructions of the Ministry of Health were fully observed.



5. Aims and overview of their fulfilment

International cooperation was focused on the activities resulting from the membership of SR in the EU structures, further on the development of the cooperation and exchange of information between member states OECD.

Another important task was the cooperation with EDQM and OMCL, in purpose of the unified implementation of the quality system in laboratories in the framework of mutual recognition of the results as well as the cooperation and participation in the regular sessions of EMEA.

The nominated representatives participated in the regular sessions of the working groups and commissions according to the requirements of European institutions (EMEA, EDQM, OECD, EC).

Legislative activity was realized within the cooperation with the Ministry of Health, Ministry of the Environment, Ministry of Economy and the Centre for chemical substances in the frame of the implementation of decisions and recommendations of OECD and European Committee in the field of chemical substances.

Quality Management was focused on the implementation of the effective system of documents control in electronical form.

During the coordination of the tasks within the unified quality systems in the purpose of the mutual recognition of results the cooperation with OMCL, EMEA and OECD proceeded. The supervision of the laboratories with SIDC authorization on the pharmaceutical and toxicologically-pharmacological testing was executed. At the same time the criteria of the quality systems were consequently applied.

Administrative Section according to the plan of the control activity realized the control activity and ensured the complaints and petitions agenda in the terms of valid legislation.

Moreover it was ensured performing of the tasks in the field of public relations and works related to the new website and new logo of SIDC. Further there were the works in the field of metrological activity and in the division of fire protection, work safety and civil defence.

Law Department issued 38 decisions imposing fines for breaking the act on medicinal products and medical devices and the act on advertisement in total sum 1 035 000,-SKK.

Informatics – the processing of the registration documentation started in new programme. The updating of the database of registered medicinal products and assignation of codes was performed continuously. In cooperation with the company MCR the work on the internal information system proceeded. The competitive bidding for purchase of electronical registry, subsequent training of staff was realized.

Registration Section activity was focused on the implementation of requirements of the revised pharmaceutical legislation EU in SR on the basis of the Act No 342/2006 Coll. which amends the act on medicinal products and medical devices in the field of registration. It involves the new organization of registration renewal process and completely new problems of patents. Further there were the tasks related to the registration applications in backlog.

Quality Assessment of Medicines Section primarily ensured the assessment of the applications in backlog. The schedule of assessment reports planning was introduced in

cooperation with the Registration Section. The Pharmacopoeia activity has continued by the translations of the paragraphs of Ph.Eur. 5th edition. Index of Latin, English and Slovak terms of European Pharmacopoeia was elaborated. The monographs to the Slovak Pharmaceutical Codex passed the expert assessment and the text was subedited to the final form.

Inspection section activity consisted of the ensuring of preparation, coordination and realization of the foreign MRA GMP audit from the side of member group of international agreement (Canada).

Analytical control activity was especially focused on quality monitoring of the random samples of medicinal preparations, purified water and packages in the view of chemical and microbiological quality.

Drug Safety and Clinical Trials section was focused on starting of electronical transmission of adverse effects reports and on entering of reports to the database Eudravigilance. Cooperation with WHO on International Drug Monitoring project and involvement to the EU system proceeded.

In the field of clinical testing of drugs and medical devices and Good Clinical Practice SIDC was providing the assessment of the applications for clinical testing, issuing the decisions on clinical testing permissions, approving of work places and conducting supervision.

Medical Devices Section has ensured the tasks connected with the registration and renewal of validity of medical devices on the basis of new EC/CE certificates. In comparison with the last year the amount of notifications of the adverse effects increased expressively. Monitoring of notifications of clinical testing of medical devices proceeded.

Economy and Maintenance section ensured the activity of SIDC connected with the monitoring of expenses of the particular units and control laboratories 1 – 5. The budget for the new investments in the volume 5 317 thousand SKK was utilized according to the investment register for 99,9%. It was enunciated the competitive bidding on the reconstruction of Control laboratory 4 Žilina, which is currently being realized.

Personnel Office – the main activity covered the realization of the Act on civil service and the act on works performed in public interest. In the evaluated year had SIDC approved totally 232 berths, thereof 91 employees in civil service and 132 employees for performing works in public interest.

6. Evaluation and analysis of SIDC development

Exacting tasks of the institute in the year 2006 were solely financed from state budget resources. These were assigned for common and capital expenses. The fulfilment of tasks has been the subject of evaluation at the sessions of the Director of SIDC and the following conclusions arised:

The utilization of the budget according to the particular items and sub items was realized in the Information System of Štátna pokladnica in compliance with assigned binding limits. Detail financial planning of the expenses of particular sections in the particular months and weeks increased the economy of utilization of the vested resources.



Total common expenses were utilized according to the approved actual budget, mainly for ensuring the material, services, energy, postage, official journeys and the maintenance of machines and information technology.

Capital expenses were utilized in the volume 22 107 thousand SKK. At the end of 2006 the institute started the reconstruction of the Control Laboratory Žilina and began the preparation of reconstruction of the Control Laboratory Košice and archive in Malacky. For the purchase of machines and equipment were utilized resources in the volume 7 995 thousand SKK.

In the framework of its activity the SIDC ensured incomes in the volume 9 655 thousand SKK, which presents the excess of assigned schedule in 1 655 thousand SKK. These incomes were delivered to the state budget together with the incomes from registration, which reached 108 901 thousand SKK.

7. Target groups

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External SIDC clients are:

- patients
- legal persons (pharmaceutical manufacturers, medical devices manufacturers, distributors of medicinal products and medical devices, etc.)
- physical persons (pharmacies, dispensaries of medical devices, etc.)
- applicants for clinical testing
- others (e.g. applicants for information, applicants for authorization)

Services provided to the clients:

- registration of medicinal products and medical devices
- issuing of licences for wholesale distribution
- issuing of permissions for clinical testing
- realization of entry inspections for pharmacies and dispensaries of medical devices

SIDC outputs are designed for and used by the Ministry of Health SR and wide range of users, especially pharmaceutical manufacturers, wholesale distribution companies of medicinal products and medical devices, owners of public and hospital pharmacies, opticians and dispensaries of medical devices, as well as the general public.

The specialized advisory services and consultancy in the field of registration of medicinal products and medical devices, issues related to Slovak Pharmacopoeia and Slovak Pharmaceutical Codex and other specialized services are provided by the particular sections and departments of SIDC.

Agenda related to Act No. 211/2000 Coll. on free access to information is centralized at the PR & Communication Division. Totally 253 requests for information were received and handled.

The editorial activity in the evaluated year was represented by quarterly publishing of the „Reports on Drug Quality“ that are published for the benefit of general medical public. The reports inform about non-compliant preparations and the measures resulting from it, eventually about products consequently released for medical use.

Electronical form of output is represented by the database of registered medicinal products being used especially by the Ministry of Health SR and health insurance companies. Partial outputs from the mentioned database are provided to the applicants for the registration and to the Ministry of Finance SR for the purpose of pricing of medicines.

8. Publication of the Annual Report

The Annual Report is published in two versions (Slovak and English language) and will be delivered to Ministry of Health of the SR, Slovak Medical University and to the other domestic and foreign institutions. The Annual Report is also published on SIDC's website www.sukl.sk.



Annex No 1

OVERVIEW OF ANALYTICAL CERTIFICATES AND SAMPLES

Total number of analytical certificates accepted **265**

Total number of applications for registration and variation in registration accepted **4.613**

Total number of samples accepted for laboratory testing **785**

Total number of registered PTS, CS – international tests **8**

Analytical certificates	Complying	Non-complying	Pending	TOTAL
Imported medicines	323	4	58	385
Domestic producers	0	0	0	0
TOTAL	323	4	58	385

Samples assessed by laboratory testing	Complying	Non-complying	Pending	TOTAL
Imported medicines	53	1	59	113

Samples assessed by laboratory testing	Complying	Non-complying	Pending	TOTAL
MIS*, Pharmacies	282	104	29	415
IMUNA PHARM HOLDING, Inc.	0	0	4	4
ZENTIVA, Inc.	149	0	8	157
CHIRANA T. INJECTA, Inc.	0	0	0	0
VULM, Inc.	47	0	21	68
Clinical complaint	9	0	8	17
Starting substances	0	0	0	0
Complaints	6	3	10	19
GALVEX, Ltd.	17	1	2	20
EL, Ltd. S.N.Ves	8	0	0	8
Clinical batch	0	0	0	0
Other companies	7	1	7	15
Centre of Drug Dependences	0	0	0	0
Attests	1	0	0	1
UP – G 5/2002	0	0	0	0
PTS, CS tests	8	0	0	8
Internal testing	16	0	5	21
TOTAL	550	109	94	753

*MIS (Manufacture of infusion solutions)

Annex No 2

OVERVIEW OF INSPECTIONS OF GDP AND GPhP DEPARTMENT

Medical facilities	Inspections	Number
Public pharmacies	Entry inspections	65
	Obligatory-concurrent inspections	1
	Targeted inspections	12
Branches of public pharmacies	Entry inspections	5
	Obligatory-concurrent inspections	0
Hospital pharmacies	Entry inspections	5
	Obligatory-concurrent inspections	0
	Targeted inspections	0
Dispensaries of medical devices	Entry inspections	13
	Obligatory-concurrent inspections	0
	Targeted inspections	5
Distribution organizations	Entry inspections	18
	Obligatory-concurrent inspections	0
	Targeted inspections	4
Opticians	Entry inspections	8
Other facilities		25
TOTAL		161



Abbreviations

ADR	Adverse Drug Reaction
CAP	Centrally Authorised Product
CMD(h)	Coordination Group for Mutual Recognition and Decentralised Procedure (human)
COMP	Committee for Orphan Medicinal Products
CP	Centralised Procedure
CRS	Chemical Reference Substance
CS	Collaborative Study
DCP	Decentralised Procedure
EDQM	European Directorate for the Quality of Medicines
EMA	European Medicines Agency
GCP	Good Clinical Practice
GDP	Good Distributing Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GPhP	Good Pharmacy Practice
ICSR	Individual Case Safety Reports
MH SR	Ministry of Health of the Slovak Republic
MHRA	Medicines and Healthcare products Regulatory Agency
MRA	Mutual Recognition Agreement
MRP	Mutual Recognition Procedure
OECD	Organisation for Economic Co-operation and Development
OMCL	Official Medicines Control Laboratories
Ph.eur.	Pharmacopoea Europaea
PIC/S Scheme	Pharmaceutical Inspection Convention Scheme
PIL	Patient Information Leaflet
PSUR	Periodical Safety Update Report
PTS	Proficiency Testing Study
QRD	Quality Review Documents
SAHP	Slovak Agency for Human Pharmacy
SIDC	State Institute for Drug Control
SOPs	Standard Operating Procedures
SPC	Summary of Product Characteristic
SR	Slovak Republic
STN ISO	Slovak Technical Norm
WHO	World Health Organisation





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