UNI
BASEL

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## INSTITUTE OF PHARMACEUTICAL TECHNOLOGY

### UNIVERSITY OF BASEL

www.pharma.unibas.ch/technology/index.html
www.mcc-online.com/presster.htm
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# PRESENTATION OF THE INSTITUTE

# PROGRESS REPORT 2001 AND OUTLOOK

# ATTACHMENT

# PRESENTATION OF THE INSTITUTE

## A. Organisation

The Institute of Pharmaceutical Technology (Head: H.Leuenberger) is part of the Department of Pharmacy of the University of Basel. The Department of Pharmacy of the University of Basel [Uni BS] forms together with the Institute of Pharmaceutics of the Federal Institute of Technology Zürich [ETHZ] the Centre of Pharmaceutical Sciences of Uni BS and ETHZ. (See the different organizational charts in the attachment). The Centre of Pharmaceutical Sciences Basel-Zürich fits well into the concept to establish and strengthen the cooperation between Swiss Universities.

## B. Location/Space

Basel and its neighbourhood is the home of the world famous pharmaceutical companies Novartis Pharma, Roche and of pharmaceutical small and medium sized enterprises as well as of the equipment manufacturer Glatt. Thus Basel provides an excellent environment for research and teaching in pharmaceutical sciences. Recently an increasing number of start-up and spin-off companies have been founded and a special platform "BioValley" was formed to stimulate the cooperation and foundation of companies in the area of biotechnology.

The Institute of Pharmaceutical Technology is located on the second and partially on the third floor of the Pharmacentre of the University of Basel. Due to its research and teaching focus, the Institute of Pharmaceutical Technology requires sufficient lab space to accommodate large-size dosage form manufacturing and processing equipment.

The necessary space was provided in the Pharmacenter and the external industrial pharmacy laboratory at the Mülhauserstrasse 49/51. A large part of the space is dedicated to the practical training of undergraduates and the planned master courses. Some of the equipment is used jointly for PhD-level research and teaching. These laboratories cannot be compared with the usual chemistry labs with which the students get acquainted already in the first year of their studies. Since the move of the Institute from the historical location in downtown Basel (Totengässlein 3), the former space and safety problems are solved.

## C. Mission

- Excellent Teaching and Research in Pharmaceutical Technology concentrating on the application of basic physical and physical-chemical principles to dosage form (or concept) design and performance evaluation affecting drug delivery.
- Contributing to the mechanistic understanding of drug formulation, processing and delivery phenomena
- Providing students with the fundamental skills for following a career in academia, in industry or in related fields such as hospital and community pharmacy or government organizations, based on a

University Diploma or PhD degree in Pharmaceutical Sciences (for industry, academia, hospital) or a Federal Diploma as a Pharmacist (for hospital and community). MAXIM: "Science fascinates us as the key for Technologies changing the world" (freely adapted from I.Asimov)

# D. Teaching

## *D. 1. Undergraduate Teaching (Diploma students)*

For the preparation of the diploma work (21 weeks) the following courses, including practical laboratory training work, are offered:

- Liquid-sterile Dosage Forms
- Semi-solid Dosage Forms
- Solid Dosage Forms

Quality assurance and GMP topics are included in the Seminar „Pharmaceutical Technology" which complements the contents of the courses mentioned. In addition, the seminar is designed for the training of the presentation skills.

Within the following years, it is planned to update the courses taking into account new learning technologies and to have the theoretical courses available in German, English and Russian language (see D. 3).

The Institute of Pharmaceutical Technology is a member of GPEN [Global Pharmaceutical Education Network] http://www.hbc.ukans.edu/phch/gpen.htm

## *D. 2. Postgraduate Teaching*

### D.2.1 Postgraduate education program (NDS) in cooperation with the Center of Pharmaceutical Sciences, Basel – Zürich.

In the frame of the postgraduate education program (NDS) of the Center of Pharmaceutical Sciences Basel-Zurich, the Institute of Pharmaceutical Technology and the Chair "Galenical Sciences" (Prof. H.P. Merkle, ETH Z) are preparing together with representatives from the pharmaceutical industry in Basel a new 6-day course on "Trends and Strategies in Manufacturing Pharmaceuticals". The majority of the speakers/lecturers will be experts from industry. The PhD students will pay a moderate fee compared to participants from industry similar to the already established course on "Quality Assurance" offered by the Center. PD Dr. G. Imanidis of the University of Basel together with Verena Renggli, a center employee, coordinate these activities, which are partly based on the former CEIP programs (Continuing Education in Industrial Pharmacy) of the Institute of Pharmaceutical Technology headed by PD Dr. G. Imanidis.

### D.2.2 Co-operation with the TTC (Technology Training Centre), Binzen

The Glatt Croup has established a special Technology Training Centre [TTC] at the Binzen Facility, Germany. Binzen is located close to Lörrach and can be reached easily with the highway from Basel in ca. 20 minutes. The Institute of Pharmaceutical Technology has a close co-operation with Klaus Eichler, head of the TTC.

The program of TTC is available at the following Web Site: http://www.glatt.de/ttc/index-d.htm.

In case, that the courses are not overbooked a limited number of graduate students can participate at the individual courses. The participation at these courses is counted as part of postgraduate education in Pharmaceutical Technology.

## *D. 3. New Learning and Teaching Technologies Co-operation with MUCTR, Moscow, Russia/Development of Curriculum*

- **Teaching:** Recently, a new Department of Technology of Chemical-Pharmaceutical and Cosmetic Products at the Mendeleyev's University of Chemical Technology of Russia (MUCTR) was founded. The co-operation Basel-Moscow has the aim to exchange expertise and to step towards the creation of a Faculty of Pharmacy at MUCTR. The program has as a goal to give Russian specialists the opportunity to strengthen the knowledge in Pharmaceutical Technology: The CD-Rom Physpharm with mathematical model equation has been successfully translated into Russian by Maxim Puchkov (MUCTR) and is part of the student education at MUCTR and at the University of Basel. Teaching Presentation: Glatt equipment: The company Glatt, Binzen, Germany is a global leader in process equipment for life sciences. The equipment and the technologies, such as fluid bed, granulating, coating, drying etc. are presented in a power point presentation and translated into Russian by Denis Shishulin, MUCTR. The teaching presentation is part of the student education in the field of modern technological equipment of pharmaceutical plants at MUCTR.
- **Development of an Expert System for Capsules and Tablets:** The primary goal of this expert system is to create a pharmaceutical formulation database for the development and manufacturing of solid dosage forms (Julia Mishina, MUCTR). In addition, statistical experimental design studies and the application of artificial neuronal networks [ANN] are used for the optimization of Pharmaceutical Dosage Forms. The idea is to use this system as a support for decision-making and as a tool in laboratory training and for development optimization.
- **Computational Science Project:** Mathematical modeling (Denis Shishulin, MUCTR) using data on Spray-Freeze Drying and data, which will be provided by the new prototype of this equipment at Glatt, Binzen in connection with the PhD-project of Mathias Plitzko on the "Preparation of Nanocomposites" in collaboration with the NCCR Nanocenter in Basel (Prof. Güntherodt, group "Nanoscience in Medicine" of Prof. U. Aebi, Biocenter of the University of Basel).

# E. Research

## *E. 1. Introductory remarks*

Our research in pharmaceutical technology concerns the design and the preparation of dosage forms for a safe transport of the active substance (drug-load) to its site of action, i.e., the precise amount of drug should be delivered at the right time at the right site in order to perform its optimal therapeutic effect (with minimal side effects)! The design, the development and the manufacture of dosage forms are often

declared in industry as the core activity or core business of industrial pharmacists since today most of them work in this area. Due to its complexity, the design of drug formulations is so far mainly based on empirical knowledge often simply using the "trial and error" approach. Thus, there is a need for action. Solid dosage forms representing the majority of prescribed medications, presently and most likely also in the future, are no exception as the science and technology of powders are still in the state of infancy. Research in the field of dosage forms being products with a high added value should therefore be rewarding.

## *E. 2. Research Focus/Objectives*

Our ambitious objective is to develop a **rigorous scientific framework for the design of formulations** and for drug processing using solid dosage forms as typical model formulations. These topics fit ideally the goals of FDA for a drug quality system for the 21th century and FDA's PAT initiative. See: xxx of the FDA event on March 28, 2003, Pharmacenter of Basel in the attachment. This focus leads to an expertise in powder technology, which is a prerequisite for a safe scale-up and for the design of novel drug delivery systems such as particles to be inhaled, i.e. for pulmonary administration. For this reason it is important to explore innovative process technologies taking into account the **opportunities of nanoscience** and nanotechnology in order to solve present problems of novel drugs such as poor water solubility and the parenteral administration of proteins. Due to the high density of pharmaceutical expertise in Basel a complementary focus in research resides in the close **cooperation with the pharmaceutical industry** including the Glatt Company as manufacturer for process equipment for the pharmaceutical industry. The goals of these activities are to create win-win situations and to compensate as much as possible the lack of university resources for the department of pharmacy at the University of Basel.

For dosage form design guaranteeing optimal drug delivery characteristics, drug specific properties such as solubility and biomembrane permeability as well as interaction of the dosage form at the site of application must be taken into account. This is a further research focus of the Institute of Pharmaceutical Technology under the guidance of PD Dr. Georgios Imanidis, Deputy Head of the Institute, with the objective to develop **models for a mechanistic understanding of drug transport through biological membranes,** notably human epidermis, intestinal epithelium simulated by the Caco-2 cell culture system and artificial phospholipid membranes, and discover **delivery system-based methods to influence it**.

## *E. 3. Research Areas*

### E.3.1 Main Areas

**Research in Powder Technology** Dry and Moist Agglomeration of Powder, i.e. Granulation, Tabletting

- Control and Scale-up of the Moist Agglomeration Process
- Computer assisted Design of Solid Dosage Forms
- Preformulation and Formulation Research

**New Process Technologies**

- Vacuum Fluidised Bed System.
- Spray Freeze Drying at Atmospheric Pressure.
- Scale-up in the 4th Dimension (Moist Agglom. and Drying Process).
- Supercritical CO2 and Liposomes
- High Temperature Short Time Sterilization

**Basic Research Activities (SNF, Industry)**

- Application of Percolation Theory and Fractal Geometry:
- Formulation Research: Robustness and Percolation Thresholds (Critical Concentrations).
- Multicomponent Formulations: Fractals and Order in a Chaotic System!
- Solubility, Structure of Water, Hydrophilic Solutions.

**Drug Absorption; (PD Dr. G. Imanidis)**

- Interface Dosage Form/Body of Patient.
- Drug Transport: Intestine/Systemic Circ.
- Transmucosal, Transepithelial Transport.
- Problem of Bioavailability of topical dosage forms.
- Problem of Drugs with a Poor Water Solubility.

Specifically, research related to Drug Absorption is subdivided into two focus areas:

1 Dermal (topical) and transdermal (systemic) delivery of drugs including low molecular weight organics and peptide analogues employing formulation design and iontophoresis as a means to modulate and enhance delivery rate.
Fundamental *in vitro* studies of the effect of phase structure in multi-phasic systems and of parameters involved in iontophoresis (pH micro-environment, electroosmotic flow, fraction of aqueous channel pathway) are undertaken, modelling processes based on physicochemical principles to allow quantitative assessment of the influencing factors. Simultaneous transport and metabolism in the skin is considered, drug concentration within cutaneous tissue is estimated and pharmacological concentration/response relationships established *in vivo* using site of action concentration as a measure of skin bioavailability.

2 Intestinal drug absorption using the Caco-2 cell line and phospholipid vesicles as model to simulate the absorption epithelium. A mechanistic approach is taken to identify the routes that are relevant for transepithelial transport of drugs and to establish possible relationships between the fluidity of the

plasma membrane of the cells and the phospholipid bilayer of the vesicles and the permeation rate. Steady state and real time fluorescence depolarisation measurements are used to obtain a measure of membrane fluidity and the effect of adjuvants such as surfactants and lipids contained in drug formulations on the membrane is evaluated. The interrelation between membrane properties and the function of efflux mechanisms such as those related to P-glycoprotein is studied and cellular pharmacokinetics considering transport and metabolism established.

## *E. 4. Research Policy*

- Problem oriented, derived from needs. (Applied and Basic Research).
- Themes, Projects are interrelated. Identification of interesting Niche Topics.
- Optimisation of Return on Investment.
- Close Cooperation with the Industry (Pharma, Equipment Manufacturer).

## *E. 5. Important Research Papers*

### E.5.1 Application of Percolation Theory and Fractal Geometry

- Percolation Theory, Fractal Geometry and Dosage Form Design, H.Leuenberger, L.Holman, M.Usteri and S.Winzap, *Pharm.Acta Helvetiae* **64:**34-39 (1989).
- The application of percolation theory in powder technology (Invited review), Hans Leuenberger, *Advanced Powder Technology* **10:**323-353 (1999)

### E.5.2 New Process Technologies

- Granulation and Drying in Vacuum Fluidised Bed Systems, B.Luy, B.Hirschfeld and H.Leuenberger, *Drugs made in Germany* **32:**3-8 (1989).
- Atmospheric Spray Freeze Drying: a suitable alternative in freeze drying technology, M.Mumenthaler and H.Leuenberger, *Int.Journal of Pharm*. **72:**97-110 (1991)
- Scale-up in the field of Granulation and Drying. Chapter 6. Bookchapter, in english. Hans Leuenberger, Drugs and the Pharmaceutical Sciences, Volume 118, ISSN 0360-2583. Pharmaceutical Process Scale-Up 118 2001, 151-170. ISBN 0-8247-0625-0. Editor(s) Levin Michael.
- New Trends in the Production of Pharmaceutical Granules: Batch versus Continuous Processing. Publication, in english. Hans Leuenberger, Eur.J.Pharm.Biopharm. 52 (3), 2001, 289-296. ISSN 0939-6411.
- New Trends in the Production of Pharmaceutical Granules: The classical batch concept and the problem of scale-up. Publication, in english. Hans Leuenberger, Eur.J.Pharm.Biopharm. 52 (3), 2001, 279-288. ISSN 0939-6411.

### E.5.3 Experimental Design; Surface Response Methodology Artificial Neural Networks; Expert Systems


- A Factorial Design for Compatibility Studies in Preformulation Work, H.Leuenberger and W.Becher, *Pharm.Acta Helv.* **50:**88-91 (1975).
- Mathematische Modellierung und Optimierung pharmazeutisch-technologischer Qualitätsmerkmale fester Arzneiformen, H.Leuenberger, P.Guitard und H.Sucker, *Pharmazie in unserer Zeit* **5:**65-76 (1976).
- Basic Concepts of Artificial Neural Networks (ANN) Modelling in the Application to Pharmaceutical Development, J.Bourquin, H.Schmidlin, P.vanHoogevest and H.Leuenberger, *Pharm.Development and Technology* **2:**95-109 (1997).


### E.5.4 Drug Delivery through Biological and Artificial Membranes


- G.Imanidis, K.C.Hartner and N.A.Mazer. Intestinal Permeation and Metabolism of a Model Peptide (Leuprolide) and Mechanisms of Permeation Enhancement by Non-Ionic Surfactants. *Int.J.Pharm.* **120:**41-50 (1995).
- G.Imanidis, C.Waldner, C.Mettler and H.Leuenberger. An Improved Diffusion Cell Design for Determining Drug Transport Parameters across Cultured Cell Monolayers. *J.Pharm.Sci.* **85:**1196-1203 (1996).
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- R.Imboden and G.Imanidis. Effect of the Amphoteric Properties of Salbutamol on its Release Rate through a Polypropylene Control Membrane. *Eur.J.Pharm.Biopharm.* **47:**161-167 (1999).


## *E. 6. Suggested Further Reading*

### E.6.1 Application of Percolation Theory and Fractal Geometry


- Fractal Dimension of Porous Solid Dosage Forms, M.Usteri, J.D.Bonny and H.Leuenberger *Pharm.Acta Helv.* **65:**Nr. 2 (1990): 55-61.
- Formation of a Tablet: A Site-Bond Percolation Phenomenon, H.Leuenberger and R.Leu *J.Pharm.Sci.* **81:**Nr. 10 (1992): 976-982.
- Matrix-Type Controlled Release Systems: I. Effect of Percolation on Drug Dissolution Kinetics, J.D.Bonny and H.Leuenberger *Pharm.Acta Helv.* **68:**(1993): 25-33.
- Percolation Effects in Matrix-Type Controlled Drug Release Systems, H.Leuenberger, J.D.Bonny, M.Kolb *Int.J.of Pharm.* **115:**(1995): 217-224.
- Use of Percolation Theory to Interpret Water Uptake, Disintegration Time and Intrinsic Dissolution Rate of Tablets Consisting of Binary Mixtures, R.Luginbühl and H.Leuenberger *Pharm.Acta Helv.* **69:**(1994): 127-134.
- Percolation Theory and Robust Formulations in Powder Technology, H. Leuenberger in Proceedings '96 China-Japan Symposium on Particuology edited by Yong Jin, Mooson Kwauk, Genji Jimbo and Yasuo Konseka, Tsinghua University Beijing May 24-25, 1996.

## E.6.2 Process Technology/Solid Dosage Form Design

- Theory of the Granulating Liquid Requirement in the Conventional Granulation Process, H.Leuenberger, H.P.Bier and H.Sucker *Pharm.Techn.Intern*. **3:**(1979): 60-67.
- Scale-up of Granulation Processes with -Reference to Process Monitoring, Acta Pharm.Techn. **2:**(1983): 274-280.
- Monitoring Mass Transfer Processes in order to control moist agglomeration, H.Leuenberger and G.Imanidis *Pharm.Techn*. **10:**(1986): 56 - 73
- Monitoring the Granulation Process: Granulate Growth, Fractal Dimensionality and Percolation Threshold, H.Leuenberger, M.Usteri, G.Imanidis and S.Winzap Boll. Chim. Pharm. **128:**(1989): 54-61.
- Agglomeration of Binary Mixtures in a High-Speed Mixer, M.Usteri and H.Leuenberger *Int.J.of Pharm.* **55:**(1989): 135-141.
- Design and Modification of Powders - A Must in Pharm. Technology, H.Leuenberger Proceed. 2nd World Congress Particle Technology, Sept. 19-22, 1990, Kyoto, Japan Vol. III. p. 317-328, The Society of Powder Technology, Japan.
- Design and Optimisation Approaches in the Field of Granulation, Drying and Coating, H.Leuenberger Pharmacy World Congress '93, Tokyo, Proceed. of the 53rd Int. Congress of Pharm. Sciences 1993, D.J.S.Crommelin, K.K.Midha, T.Nagai editors, Medpharm. Scientific Publishers, Stuttgart 1994, p. 493-511.

## E.6.3 New Process Technologies

- Prozess Monitoring bei der Emulsionsherstellung Drehmomentenmessung als In Prozess Kontrolle bei der Emulsionsherstellung, R.Randegger, G.Imanidis, R.D.Juch, G.Birrenbach, H.Leuenberger *Pharm.Ind.* **56:**(1994): 648-654
- Wet spherical agglomeration of proteins as a new method to prepare parenteral fast soluble dosage forms, A.Bausch and H.Leuenberger *Int.J.of Pharm*. **101:**(1994): 63-70
- List of Preparation of Liposomes Encapsulating Water Soluble Compounds Using Supercritical Carbon Dioxide, L.Frederiksen, K.Anton, P.vanHoogevest, H.R.Keller and H.Leuenberger *J.Pharm.Sci.* **86:**(1997): 921 –928.
- Thermal Sterilization of Heat Sensitive Products using High-Temperature Short-Time Sterilization, A.Mann, M.Kiefer and H.Leuenberger, *J.Pharm.Sci,* **90**:(3), 275-287 (2001).

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- P.Lütolf, G.Imanidis and H.Leuenberger. Transdermal Iontophoresis of an Amphoteric Compound: Effect of Charge and Interaction with Human Skin, In: P.Couvreur, D.Duchéne, P.Green and H.E.Junginger (Eds.), Transdermal Administration, A Case Study, Iontophoresis, Editions de Santé, Paris, 1997, pp. 360-364.
- G.Imanidis and R.Imboden. Utilizing Vehicle Imbibition by a Microporous Membrane and Vehicle Viscosity to Control Release Rate of Salbutamol, *Eur. J. Pharm. Biopharm.* **47:**283-287 (1999).
- F.P.Schwarb, G.Imanidis, E.W.Smith, J.M.Haigh and C.Surber. Effect of Concentration and Degree of Saturation of Topical Fluocinonide Formulations on *In Vitro* Membrane Transport and *In Vivo* Bioavailability on Human Skin. *Pharm. Res.* **16:**909-915 (1999).

## *E. 7. Publications: Institute of Pharmaceutical Technology 1997-2001*

**1997**

An extended model based on the modified Nernst-Planck equation to describe transdermal iontophoresis of amphoteric compounds. Proceedings, in english. Georgios Imanidis, Peter Lütolf, Hans Leuenberger, ISSN 1022-0178. Proc.24th Int.Symp.Controlled Release Bioact.Mater. 1997, 29-30. 24th International Symposium on Controlled Release of Bioactive Materials; Stockholm 15.06.97 - 19.06.97.

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**2000**

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**2001**

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Evaluation of flow properties of dry powder inhalation of salbutamol sulfate with lactose carrier.. Publication, in english. Kotaro Iida, Youhei Hayakawa, Hirokazu Okamoto, Kazumi Danjo, Hans Leuenberger, Chem.Pharm.Bull. 49 (10), 2001, 1326-1330. ISSN 0009-2363.

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Method for producing particulate goods. Patent Specification, in german. Hans Leuenberger, Armin K.T. Prasch, Bernhard Luy, PCT Int. Appl. 2001, 1-54.

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Scale-up in the field of Granulation and Drying. Chapter 6. Bookchapter, in english. Hans Leuenberger, Drugs and the Pharmaceutical Sciences, Volume 118, ISSN 0360-2583. Pharmaceutical Process Scale-Up 118 2001, 151-170. ISBN 0-8247-0625-0. Marcel Dekker Inc., Editor(s) Levin Michael.

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Thermal Sterilization of Heat Sensitive Products using High-Temperature Short-Time Sterilization. Proposal, in english. Angelika Mann, Markus Kiefer, Hans Leuenberger, J.Pharm.Sci. 90 (3), 2001, 275-287. ISSN 0022-3549.

## *E. 8. Contribution by External Docents (see also attachment)*

- Prof. Theodor Güntert, PhD, having important responsibilities in his job at Roche Basel is lecturing Biopharmaceutical and Pharmacokinetic topics and is supervising a tutorial with practical applications of Pharmacokinetic data. The list of his publications in 2001 can be found in the attachment.
- PD Danièlle Giron, PhD, is expert and head of the Thermoanalytic laboratory at Novartis Pharma Ltd. Her contribution teaching thermoanalytical topics is highly appreciated. Her publications are listed in the attachment.
- PD Peter van Hoogevest, PhD, is an expert in the formulation and the manufacture of liposomes. He recently became CEO of Phares Drug Development Ltd., Muttenz, a company specialised in liposomal technologies and applications. He is teaching liposomal related topics (including practical training) at the Institute of Pharmaceutical Technology.
- PD Stephan Marrer, PhD, responsible for the production of solid dosage forms at Roche, is teaching Quality Assurance topics and is tutor in the seminar for Pharmaceutical Technology. He has submitted his scientific oeuvre at the Faculty of Natural Sciences to become Private Docent (PD) at the University of Basel.
- Ottheinrich Eichhorst, PhD, Dr. has completed his study as a Pharmacist in 1999 and started to collaborate in 2000 with the Institute of Pharmaceutical Technology.
- Klaus Eichler is head of the Technology Training Centre at Glatt GmbH in Binzen, BRD. He is an excellent organiser and moderator of Meetings, Workshops and Symposia world-wide. The Institute of Pharm. Technology is proud of working with him for years.
- Claudia Reinke, PhD, has a degree in biology (PhD) and pharmacy (diploma). She owns the company MedSciences, Basel.
- PD Michel Ulmschneider, PhD, is private docent at the Université de Haute Alsace, Mulhouse and is supervising for the PhD thesis of Lars Sukowski at Roche.
- Bernd Herzog, PhD, is head of several R+D application labs at Ciba Specialty Chemicals, Grenzach-Wylen within the segment of home and personal care (main focus on sun screens for skin protection).

# F. Curriculum Vitae

## *F. 1. G. Betz*

**Personal information:**

| | |
|---|---|
| Date of birth | 27th of February 1971 |
| Place of birth | Ravensburg/Germany |

**Education:**

| | |
|---|---|
| 1990 | Allgemeine Hochschulreife (Abitur) at Matthias Erzberger Schule, Biberach/Riss, Germany |
| 1990-1996 | Pharmacy studies at Albert Ludwig University, Freiburg, Germany<br>Practical year at Ciba AG, Wehr, Germany and<br>Apotheke Stadtmitte, Stuttgart, Germany |
| 1996-2000 | Ph.D. study under the supervision of PD. Dr. G. Imanidis and Prof. Dr. H. Leuenberger at Institute of Pharmaceutical Technology, University of Basel, Switzerland with the title:<br>"Heparin Penetration into and Permeation through Human Skin from Aqueous and Liposomal Formulations In vitro and Interactions of Phospholipids with Skin." |

**Professional activities:**

| | |
|---|---|
| 1996-2000 | Lectureship in practical university courses of the liquid sterile dosage forms and liposomal formulations.<br>Lectureship and workshop in oral scientific presentation technique and body language. |
| 2001-2002 | Postdoctoral-fellow and head teaching assistant under Prof. Dr. H. Leuenberger at Institute of Pharmaceutical Technology, University of Basel, Switzerland. |
| Since 2002 | Head of the Industrial Pharmacy Lab and head teaching assistant at Institute of Pharmaceutical Technology, University of Basel Switzerland. |

## F. 2. G. Imanidis

| | |
|---|---|
| Georgios Imanidis, June 8, in Serres, Greece | born 1958 |
| **EDUCATION** | |
| High school (gymnasium) education with emphasis on sciences in Serres, Greece | 1973 – 1976 |
| University admission examination | 1976 June |
| Pharmacy studies at the Aristotelion University of Thessaloniki, Thessaloniki, Greece | 1976 – 1980 |
| Graduation with the Pharmacy degree | 1980 Nov. |
| Post-graduate studies in Pharmaceutical Technology and Industrial Pharmacy at the „Pharmazeutisches Institut“ of the University of Basel, Basel, Switzerland | 1980 – 1982 |
| Advanced diploma in Pharmaceutical Technology, | 1982 Dec. |
| Ph.D. thesis in Pharmaceutical Technology under the supervision of Prof. H. Leuenberger at the „Pharmazeutisches Institut“ of the University of Basel, Basel, Switzerland | 1983 – 1986 |
| Doctor of Philosophy degree | 1986 Feb. |
| **PROFESSIONAL APPOINTMENTS** | |
| Part-time (50%) teaching assistant in Pharmaceutical Technology at the „Pharmazeutisches Institut“ of the University of Basel, Basel, Switzerland | 1983 – 1986 |
| Post-doctoral fellow in Drug Delivery Research under Prof. W.I. Higuchi in the Department of Pharmaceutics, University of Utah, Salt Lake City, UT, U.S.A. | 1986 – 1988 |
| Senior research scientist in the Department for Drug Absorption Studies, TheraTech, Inc., Salt Lake City, UT, U.S.A. | 1988 – 1990 |
| Adjunct staff scientist in the Department of Pharmaceutics, University of Utah, Salt Lake City, UT, U.S.A. | 1988 – 1990 |
| Recipient of a scholarship from the Roche Research Foundation to study drug absorption using cell cultures as an alternative to animal experiments at the „Pharmazeutisches Institut“ of the University of Basel, Switzerland | 1991 – 1992 |
| Scientific staff member, „habilitand“, and head teaching assistant at the „Pharmazeutisches Institut“ of the University of Basel, Department of Pharmaceutical Technology, Basel, Switzerland | 1992 – 1999 |
| Awarded the title of a docent „PD“ by the Faculty of Natural Sciences of the University of Basel through the process of „Habilitation“. | 2000 |
| Faculty member (full time) at the Institute of Pharmaceutical Technology, University of Basel, Switzerland, by virtue of the docent "PD" title awarded by the Faculty of Natural Sciences of the University of Basel through the process of "Habilitation". | since 2000 |

## *F. 3. H. Leuenberger*

| | |
|---|---|
| **EDUCATION** | |
| Diploma in Experimental Physics (University of Basel) | 1967 |
| PhD-Thesis in Nuclear Physic (University of Basel) | 1971 |
| **INDUSTRIAL CAREER** | |
| Head of R+D Laboratory (Preformulation work)<br>Analytical R+D Department, Sandoz Ltd., Basel | 1971-1973 |
| Research Group Leader, Pharmaceutical R+D, Sandoz Ltd., Basel | 1973-1982 |
| **SABBATICALS AND EXPERIENCES ABROAD** | |
| University of Hamburg (Prof. Dr. H. Sucker) Germany | 1973 |
| University of Michigan, Ann Arbor (Prof. Dr. W.I. Higuchi, Prof. Dr. N.F. Ho, Dr. E.W. Hiestand), U.S.A. | 1979 |
| Head Pharma R+D, Sandoz España, Barcelona ad interim (Spain). | 1980 |
| **CAREER IN ACADEMIA** | |
| Part Time Lecturer at the University of Basel as Private Docent (PD) in Pharmaceutical Technology | 1980 |
| Full-Time Ordinary Professor of Pharmaceutical Technology and Head of the Institute of Pharmacy at the University of Basel, Totengässlein 3, CH-4051 Basel (Historical Site close to the Museum) | 1982 |
| Planning of a new building for the Institute of Pharmacy | 1982-2000 |
| Member of the Expert Group 12 (Pharmaceutical Technology) of the European Pharmaceutical Commission, Strasbourg, France | 1988-1993 |
| Dean of the Faculty of Natural Science at the University of Basel, Founder of the Faculty Committee of Department Heads | 1994/95 |
| President of the Scientific Council [SC] of the Swiss Academy of Engineering Science [SATW] and founder of the Lateral Think Tank of the SC | 1992-96 |
| Vice President of the Swiss Academy of Engineering Science | 1993-2001 |
| President of the Swiss Society of Pharmaceutical Sciences (SGPhW) | Since Oct. 2001 |

Member of Editorial Advisory Board (such as J.Pharm.Sci. 1990/92),
Referee for different journals,
Member of peer review committees: ETHZ (1993),
University of Groningen and Utrecht (1997),
Publications: more than 180,
Patents: ten.

### *F. 4. Research Awards, Medals, Nominations (Membership Awards)*

H. Leuenberger, on behalf of the Institute of Pharmaceutical Technology:

❖ Member of Swiss Academy of Engineering Sciences since 1987.

❖ University of Helsinki Medal 1989.

❖ Fellow of the American Association of Pharmaceutical Scientists [AAPS] since 1990.

❖ AAPS Research Award in Pharmaceutical Technologies 1993.

❖ Innovation Award for New Process Technologies of the Governments Basel-City and Basel-Country 1994.

❖ Honorary Member of the Swiss Society of Industrial Pharmacists [GSIA] since 1994.

❖ Jörg Bider Medal of the Swiss Society of Pharmacists [SAV] 1997.

❖ Corresponding Member of the Royal Academy of Pharmacy of Spain since 1998.

❖ Foreign Member of the Russian Academy of Engineering Sciences since 1998.

❖ IPS Medal 2000 [Industrial Pharmacy Section] of FIP [Féderation International Pharmaceutique]. 2000.

❖ Member of the Scientific Advisory Board of the Grand École des Mines, Albi, France, since 2001.

❖ Award of Particulate Preparations and Design of the Society of Powder Technology of Japan, Kyoto, Japan, 2001

❖ Honoraty member of the Swiss Academy of Engineering Sciences since 2001.

## G. Research and Co-operation Network

### *G. 1. Academia*

China Pharmaceutical University, Nanjing, P.R. China*

Federal Institute of Technology [ETH] Zürich*

École des Mines, Albi, France*

Gifu Pharmaceutical University, Gifu Japan*

Institute of Hospital Pharmacy, Basel

Institute of Informatics, University of Basel

* Based on formal agreements. (Activity depending on projects, time and ressources).

Mahidol University, Bangkok, Thailand*

Mendeleyev University of Chemical Technology of Russia [MUCTR], Moscow*

Spitalapotheke, Kantonsspital Aarau

University of Kansas, Lawrence, Kansas, USA*

University of Seville, Seville, Spain*

## *G. 2. Industrial Partners*

ADD, Advanced Drug Delivery Technologies, Muttenz

Asulab AG, Neuchâtel

Bachem AG, Bubendorf

Capsugel Ltd., Arlesheim

Ciba Specialty Chemicals, - Grenzach D

Drossapharm AG, Arlesheim

Glatt AG, Pratteln

Glatt GmbH, Binzen, BRD

Glatt, System Techniques, Dresden, BRD

Mepha AG, Aesch

Novartis Animal Health Ltd, Basel

Novartis Pharma Ltd., Basel

Pentapharm AG, Aesch

Pfizer GmbH, Arzneimittelwerk Gödecke, Freiburg i.Br.

Phares Ltd., Muttenz

Roche Ltd., Basel

Roche Ltd., Grenzach, BRD

Skye Pharma, Muttenz

Spirig AG, Egerkingen

* Based on formal agreements.

# H. Progress Report 2002

## *H. 1. Special Events 2002*

### H.1.1 Special Presentations and Visits at the Pharmacenter

The new Pharmacenter is a show case and its well equipped large lecture hall provides an excellent platform for special lectures for experts of the international science community. on February 5, Dr. Robin Batterham, Chief Scientist of the Commonwealth of Australia, member of the Prime Minister's Science, Engineering and Innovative Council, gave the lecture on "Transforming research into commercial activity: An Australian viewpoint". The members of the "Handelskammer beider Basel" were invited to attend this lecture as well. A special highlight was the visit of Helen Winkle and Dr. Ajaz Hussain from the FDA (US Food and Drug Administration) on February 11 and 12, visiting the labs of the Institute of Pharmaceutical Technology and the Technology Service Center at the Pfizer/Goedecke plant in Freiburg, Germany, with the novel "Multicell" production equipment avoiding scale-up problems, a result of a cooperation between the Institute of Pharmaceutical Technology , the Glatt Company as an equipment manufacturer and the pharmaceutical industry. It has to be kept in mind, that Scale-up processes can lead so weak points having adverse effects on the quality of drugs (see also the book "Pharmaceutical Process Scale-Up" 118 2001, ISBN 0-8247-0625-0. Marcel Dekker Inc., Editor Levin Michael with the book chapters: "A Collaborative Search for Efficient Methods of Ensuring Unchanged Product Quality and Performance During Scale-Up of Immediate-Release Solid Oral Dosage Forms" by A.Hussain, FDA and "Scale-up in the field of Granulation and Drying" by H.Leuenberger, University of Basel). Dr. Ajaz Hussain's presentation at the Pharmacenter wit the title "Pharmaceutical Quality: Challenging Opportunities" fits well into the new policy of the FDA to create a new drug quality system of the 21st century and provided a basis for launching FDA's PAT (Process Analytical Technology) Initiative. There is an increasing interest in the seminar on Drug Discovery & Development, Frontiers in Pharmaceutical Sciences held at the Pharmacenter. The institute of pharmaceutical technology organized the following presentations:

- May 24 2002: Public inauguration lecture of Dr. Stephan Marrer; Quality Management in the Pharmaceutical Industry.
- June 5 2002: Seminars on Drug Discovery & Development, Prof. Dr. Ueli Aebi; Imaging, measuring and manipulating biological matter from the micrometer to the nanometer scale.
- November 20 2002: Seminars on Drug Discovery & Development; Dr. Branco Weiss; Is viability a problem for new drug companies?

### H.1.2 GPEN-Meeting, University of Michigan, Ann Arbor, USA

G. Imanidis was coordinator and chairman of an intensive one-day course held at the Global Pharmaceutical Education Network Meeting GPEN2002, Ann Arbor, MI, USA, November 6-8, 2002 on Dermal and Transdermal Drug Delivery comprising ten lectures given by six international experts.

### H.1.3 New pharma business opportunities in Russia, modernisation of the russian pharmaceutical industry

During the "St. Petersburg Dialogue" between president V.Putin and Chancellor G.Schröder a satellite symposium on the modernization of the russia pharmaceutical industry was held in Weimar, on April 9, 2002. Leading scientists, experts and governmental representatives from Germany and Russia discussed actual issues concerning the modernization of the pharmaceutical industry in Russia. Russia's industry is strong in manufacturing antibiotics and vaccines. The symposium was chaired by Hans Leuenberger, as a neutral Swiss citizen and attended by high ranking VIPs from Germany and Russia.

### H.1.4 4th German Edition of the textbook "Martin Physikalische Pharmazie - Pharmazeutisch angewandte physikalisch-chemische Grundlagen"

After an intensive revision and preparation of a special CD-ROM with its collection of important equations as attachment of the book the 4th german edition of the well-known textbook

- „Martin Physikalische Pharmazie - Pharmazeutisch angewandte physikalisch-chemische Grundlagen"

was published in 2002 by the "Wissenschaftliche Verlagsgesellschaft mbH", Stuttgart, Germany. The editor of this textbook (Hans Leuenberger) would like to thank especially the collaboration of Dr. Ottheinrich Eichhorst, and Michael Lanz, pharmacist and author of the CD-ROM "Physical Pharmacy" providing a tool to visualize and to work with the most important mathematical models in the area of physical pharmacy.

### H.1.5 Edition of the proceedings of the CASS 2000 Symposium "Rise and Fall of Megatrends in Science"

In the year 2000 CASS (Conseil des Académies Scientifiques Suisses) organized in Bern a special symposium with the title "Rise and Fall of Megatrends in Science". The speakers covered themes of the four Swiss academies being represented by CASS (Engineering Sciences, Humanities, Medicine and Natural Sciences). The ideas was to discuss the origin and the driving forces being responsible for emerging trends in science and technology leading to megatrends having a tremendous impact on society. The speakers covered themes of the four Swiss academies being represented by CASS (Engineering Sciences, Humanities, Medicine and Natural Sciences). The proceedings were edited by Margrit Leuthold, Hans Leuenberger and Ewald Weibel, members of the Council of the Swiss Scientific Academies (CASS ) and published by Schwabe & Co. AG, Basel in 2002.

## H.1.6 Official Opening of the Industrial Pharmacy Lab (IPL) 26.11.2002 and Inauguration of the installation of the Presster Equipment sponsored by Pfizer Ltd.

### Mission and Research Focus of IPL

The mission of the Industrial Pharmacy Lab is to focus on research in process technology and dosage form design. This research is very close to the today's needs of the pharmaceutical industry looking for robust formulations and process technologies, which should enable to shorten the development time and to increase the product quality. A close cooperation with the pharmaceutical industry is a prerequisite to be able to do studies in the area of scale-up. Thus a win-win situation is created as there is no time for basic studies in scale-up in the industry and there is no large scale equipment for such studies at the university. This concept is very unique!

Our research is working to understand and control pharmaceutical processes, such as tabletting, capsule filling, moist agglomeration, atmospheric spray-freeze-drying, and protein degradation during filling and dosing. Furthermore our aims are to design and develop new devices to improve the pharmaceutical processes and avoid scale-up problems.

The Industrial Pharmacy Lab with its equipment is an excellent place to be strongly involved in the implementation of the planned master courses in Pharmaceutical Technology and Industrial Pharmacy. As industrial sized equipment we find actually a capsule filling machine (sponsored by Pfizer), equipment for manufacturing granules (sponsored by Glatt) and different types of tabletting machines. The so-called "Presster$^{R}$" is a special compaction equipment to simulate high-speed tabletting machines but consuming only a small amount of material. This equipment is sponsored by Pfizer and is related to a new Ph.D. project in solid dosage forms (see following chapter).

## Solid dosage forms

### Pfizer Freiburg collaborates with the University of Basel, Switzerland on the Topic of Compaction Simulation

Since many years Pfizer Freiburg successfully collaborates with Prof. Dr. Hans Leuenberger, Head of the Institute of Pharmaceutical Technology, Pharmacenter, University of Basel, Switzerland. Based on this interaction a mutual strong relationship was developed.

Nearly one and a half years ago Pfizer Freiburg decided to buy the Presster$^{R}$, a compaction replicator supplied by MCC (Metropolitan Computing Corporation), East Hanover, New Jersey and install it at the Industrial Pharmacy Lab of the Institute of Pharmaceutical Technology, Pharmacentre, University of Basel, Switzerland.

The Presster[R] is a single station high-speed tablet press, which is capable to simulate the performance of high-speed rotary tablet presses with a minimum of tabletting material.

Thus the following win-win situation is created:

Prof. Dr. Hans Leuenberger supervises the project (Ph.D. thesis Anja Guntermann) with the aim to compare the results obtained by compaction simulation trials with various high-speed rotary tablet presses used for routine production at the Pfizer Freiburg plant.

The sponsoring of Pfizer also supports the community putting Pfizer values into action. Young students will also participate on this new type of equipment during their education. Needless to say that Basel is the first European university providing their students such type of equipment sponsored by Pfizer.

The Ph.D. project of Anja Guntermann looks at different compaction profiles, which can be simulated by the Presster[R] and analyses the capability of this equipment to make predictions of the performance of a formulation on high-speed tabletting machines. Thus, at the same time two goals can be pursuit: research in dosage form design and in scale-up of manufacturing processes. This is an important point as Pfizer Freiburg is one of the key sites involved in the Co-Development-Process for new solid oral products.

The studies with the Presster[R] equipment are applicable during the product development and scale-up phase of new products as well as supporting continuous improvement and optimization of marketed products.

## Moist Agglomeration of Powder, Control and Scale-up of the Process

This research is relevant to the pharmaceutical industry, where the granulation process is an important step in tablet production. A constant quality of granules is a key factor in robust dosage form design. A change in the granule size distribution, final moisture content, friability, compressibility and compactibility of the granules may strongly influence the properties of the final tablet such as tablet hardness, tablet friability, disintegration time, dissolution rate of the active substance etc.

The experimental studies are performed using high-shear mixers and fluid bed equipment. We employ various techniques such as power consumption measurement, acoustic signal determination and tensile strength measurement during granulation. During the Ph.D. thesis work of Pascale Junker a computer program was developed in cooperation with Pharmatronic AG, Pratteln, Switzerland to control granulation "in process". We have introduced the turning point of the power consumption profile as a signature of the starting material and furthermore as a parameter for the cohesiveness of the starting material and therefore for optimal end-point detection at an early stage.

**Technological Applications**

In order to avoid scale-up problems and to reduce time to market, continuous or semi-continuous processes have to be evaluated as alternatives to a batch production.

A quasi-continuous production concept can take into account the advantages of a batch-type and a continuous process. Such a concept for granulation and drying was developed in co-operation with the Institute of Pharmaceutical Technology of the University of Basel, Glatt Ltd., CH-4133 Pratteln and F. Hoffmann-La Roche Ltd., CH-4070 Basel.

The result of this concept is the Glatt Multicell equipment, which became first operative at the Roche production site. A further developed version has been installed at the Technical Service Center at Goedecke (Pfizer Group) in Freiburg, Germany.

## Solid Dispersions to Enhance the Dissolution of Poorly Water-Soluble Drugs

Increasing numbers of drug candidates have poor bioavailability caused by low aqueous solubility. Solid dispersion (SD) is one of the effective approaches to enhance solubility. Although many studies on SDs have been reported in literature, it is still not common in pharmaceutical industry and commercial examples are rare. Instability of SDs is one of the main reasons and therefore the development of SDs is challenging.

In cooperation with Shionogi & Co., Ltd., Japan two general preparation methods, organic solvent method and fusion-quench method are investigated and compared (visiting scientist Hiroshi Tanaka). As a model drug indomethacin is used with the aim of establishing a methodology to design solid dispersions.

## Atmospheric Spray-Freeze-Drying

The production of Nanocomposites using the spray-freeze-drying technique is a Ph.D. project in cooperation with Glatt GmbH, Binzen, Germany in order to design a new Spray-Freeze-Drying Equipment (Ph.D. Thesis Matthias Plitzko) to be manufactured by Glatt. The project is funded by NCCR (National Center of Competence in Research) Nano-Center, Basel and Glatt GmbH.

Atmospheric freeze drying of spray frozen particles is a process to the best advantage and eliminates the typical problems of a classical freeze drying process. The considerable advantages are higher heat transfer, shorter process times and no problems with the generation and maintenance of the vacuum.

This Ph.D. Thesis is a continuation of the works KAHN (1987), MUMENTHALER (1990) and MENNET (1994) with the aim to optimize the Atmospheric spray-freeze-drying process concerning the process time and the properties of the final product. Furthermore, the main focus is dedicated to the development of protein formulations. The spray freezing step of the process allows to produce very small particles (10µm and smaller) with low density suitable for powder inhalation applications.

## Liquid-sterile dosage forms

### Investigation of Protein Degradation caused by Shear Stress during Filling and Dosing Processes

Due to the recent progress in genomics, proteomics, and biotechnology pharmaproteins became more and more popular as new drug substances. The processing of these new drugs lead to new challenges as these drugs can degrade during the processing. The investigation of protein degradation during filling and dosing processes is a Ph.D. project in cooperation with Alphacos SA, Courroux, Switzerland.

The aim of this project (Ph.D. thesis Ursula Bausch) is to investigate the effect of shear forces, which occur during filling and dosing with rotary piston pumps on protein solutions. According to literature such shear forces often have a negative influence on the quality of the final product as they can cause protein denaturation. The influence of different parameters in respect to filling equipment on one hand and formulation on the other hand is examined.

As a first test substance the enzyme lactase has been chosen, since the loss of catalytic activity, which is measured by a photo spectroscopic method, can be utilized to determine the degree of protein denaturation.

Because of growing demand for protein solutions, and the problems, which could appear during filling and dosing processes, great interest is directed to the project. A cooperation proposal from Roche, Basel, Switzerland has been signed recently.

## Cooperation with Mendeleyev University of Chemical Technology of Russia (MUCTR)

### Computational Science

Within the framework of the cooperation with the Cybernetic Department of MUCTR and the Institute of Pharmaceutical Technology at the University of Basel a Russian visiting scientist (Dr. Maxim Puchkov) is working in the area of Computational Science. This cooperation is involving the creation of a virtual lab-training environment built on rule-based expert system shell with a combination of artificial neural network packages and learning management system. This environment is a part of "Neue dynamische Lehr- und Lernumgebung zur Verbesserung der internationalen Pharmazieausbildung (VIP-Projekt)". It allows experimental and theoretical data knowledge acquisition and storage within the expert system knowledge database to be accessible as training and scientific tool.

Current development is the implementation of a learning management system (LMS) at the Institute of Pharmaceutical Technology, University of Basel on the base of WebCT and Microsoft LRN software with support of URZ (Universitätsrechenzentrum). This LMS provides powerful capabilities for course content management, tracking students' activity and their progress.

### Development of a Knowledge Based System for Solid Dosage Form Design

The development of a knowledge based system for solid dosage forms is a Ph.D. project within the framework of the cooperation with MUCTR.

The aim of this project (Ph.D. thesis Johannes von Orelli) is to develop a computer program that is a valuable tool for decision making and for choosing the optimal and robust formulation (research in dosage form design). Typically, such a system contains a knowledge base describing solid dosage forms to facilitate the design of novel dosage forms. Thus, in order to save time and money in the formulation process of a tablet or a capsule, knowledge based systems can be used. After defining for example distinct physical characteristics of the active substance, the excipients, which can be used in the formulation and the properties of the product, the knowledge based system gives a suggestion for a formulation.

At first a number of experimental data should be collected with a variety of specific model drugs according to the Biopharmaceutical Classification System, representing 4 classes: high solubility/high permeability, high solubility/low permeability, low solubility/high permeability, and low solubility/low permeability. Due to the equipment (compaction simulator, Presster$^{R}$ and capsule filler) of the industrial pharmacy lab real industrial scale can be simulated.

## *H. 2. Home page of the Institute of Pharmaceutical Technology, IT-Support*

The IT-Support for the computer network is playing an increasing role. The work of T.Kuny, M.Lanz and M.Sutter, graduate-students and responsible for IT-support, respectively for the home page is specially acknowledged.

## *H. 3. Teaching*

The intensive lab training in Pharmaceutical Technology has been widely considered by the Pharmaceutical Industry as a major strength of pharmacists originating from the University of Basel not needing a lengthy "training on the job". In addition, the interweaving of research and teaching topics and the double appointment of scientific staff as researchers and teachers has been beneficial for the students. A further strength has been traditionally and consistently the unique opportunity in Basel to recruit experts from the pharmaceutical industry as lecturers and advisors for special educational projects. There has been so far little experience with the new curriculum that is currently being established, to make a safe assessment of its effects. We are interested to see the results of the implementation of this curriculum, which leads to a significant reduction of the time spent by the undergraduate students in the labs of the Institute of Pharmaceutical Technology. We expect, however, that the introduction of a master's degree in Pharmaceutical Sciences with focus in "Pharmaceutical Technology" and "Industrial Pharmacy" as a specialization will be very attractive both for students and for the Pharmaceutical Industry. Such a master's program can be established independently, i.e. can be very flexible, as it does not depend on the jurisdiction of the federal government.

## H.3.1 New Learning Technologies

**Introduction of new learning and teaching technologies** in collaboration with the Mendeleyev University of Chemical Technology of Russia, MUCTR, Moscow and exploring of distant learning technologies. It is an objective to intensify the cooperation with the sister chair at the ETH Zurich (Hans-Peter Merkle) in the area of postgraduate and continuous education and to expand the telepoly activity. It is planned to teach "Quality Assurance" to both students in Basel and Zurich by telepoly in 2003 (PD Dr. S. Marrer, Roche). **Introduction and Implementation of master courses** with special focus in Pharmaceutical Technology and Industrial Pharmacy. The vision for such master programs includes modules which can be combined and which are offered by other departments such as the Biocenter, the Department of Chemistry, the NCCR Nanocenter and by other faculties such as modules, which are part of a master in Business Administration. It is a plan to present the master courses in english in order to attract also more students from abroad and to intensify the international collaboration (see H.3.2).

## H.3.2 International collaboration

A major goal is to intensify the existing collaborations and to implement the new collaboration with the FDA office of research and testing (Rockville, USA). It is the objective to form a research network of those research groups having already a close cooperation with this FDA office such as the MIT, the University of Maryland, the University of Michigan (Ann Arbor) being involved in the development of FDA's BCS (Biopharmaceutical Certification) System and the University of Purdue (some more may follow). It is important to realize the necessity to improve the pharmaceutical manufacturing processes as compared with processes in other industries such as the automotive industry and the semiconductor industry (2 sigma versus 6 sigma performance). Many new drug delivery ideas failed because of the lack of a possibility for large scale manufacturing. It is a goal to promote the international exchange of researchers and teachers and to increase the number of visiting scientists in Basel especially those supported by the sending party abroad (university or enterprise).

## H.3.3 Diploma Studies

In the year 2002 14 students have completed this diploma work in the area of Pharmaceutical Technology. Diploma studies were performed in the Pharmacentre as well as in laboratories of partner institutions (see H.3.4., List of diploma thesis students, topics and location).

## H.3.4 List of Diploma Students

### with diploma thesis topics in Pharmaceutical Technology 2002

| **Student** | | **Topic** | **Supervisor/Location** |
|---|---|---|---|
| Allemann | Sabin | In-vitro Modell für topische Arzneiformen | S.Wieland-Berghausen, Novartis Animal Health AG, Basel |
| Amacker | Sonja | Entwicklung und Herstellung von Lactase Pellets | T.Kuny Institute of Pharmaceutical Technology, University of Basel |
| Blaser | David | HPLC-MS Untersuchung zur Metabolismus und Permeation von Amentoflavon in Caco-2 Zellen | G.Imanidis Institute of Pharmaceutical Technology, University of Basel |
| Heigold | Barbara | Einflussnahme von Hilfsstoffen resp. Formulierungskomponenten auf die Verteilung von Wirkstoffen im Blut | B.Galli O.Kretz Novartis Pharma AG, Basel |
| Hilfiker | Marc | Neue Lerntechnologie, PharmTechKurs FlüssigSterileArzneiformen | M.Walter, H.Leuenberger Institute of Pharmaceutical Technology, University of Basel |
| Hofer | Renate | Einfluss von Komposition und Prozessparametern auf die Freisetzung von Proteinen aus Mikropartikeln | J.D.Bonny O.Lambert Novartis Pharma AG, Basel |
| Hofmann | Sandra | Applikationssysteme für die Lokalisierung von Mikrosphären am Wirkort | V.Luginbühl, H.P. Merkle, ETH Zürich |
| Mathis | Katrin | Einflüsse der Tablettenformulierung auf die Feuchtagglomeration | G.Betz, Institute of Pharmaceutical Technology, University of Basel |
| Pellanda | Carolina | Bioverfügbarkeit von Triamcinolonacetonid in der Haut | C.Surber, V.Figuereido, Institute of Hospital Pharmacy, University Hospital Basel |
| Schlatter-Häner | Chantal | Anwendung der isothermen Mikrokalorimetrie für Stabilitäts- und Kompatibilitätsuntersuchungen | M. Schmid F. Hoffmann - La Roche AG, Basel |
| Schlatter-Häner | Philipp | Gezielte Kristallisation pharmazeutischer Wirkstoffe: Kontrolle von Partikelgrösse, Habitus und polymorpher Form | R.Hilfiker B.Siebenhaar, Solvias AG, Basel |

| | | | |
|---|---|---|---|
| Voelker | Eva | Anwendung eines neuen Modells der Pulverkompression | M.Lanz, Institute of Pharmaceutical Technology, University of Basel |
| Vuong | Hoa | Bioverfügbarkeit von Sonnenschutzfiltern in der Haut | T.Tassopoulos, V.Figuereido C.Surber, G. Imanidis Institute of Hospital Pharmacy and Institute of Pharmaceutical Technology, University of Basel |
| Zurbriggen | Fabienne | Einfluss der Mambran-Fluidität von Caco2-Zellen auf den Wirkstofftransport | G.Imanidis Institute of Pharmaceutical Technology, University of Basel |

## *H. 4. Advanced activities in learning and teaching at Institute of Pharmaceutical Technology University of Basel and Mendeleyev University of Chemical Technology of Russia*

This project is joint activity between Institute of Pharmaceutical Technology of University of Basel (Prof. Dr. H. Leuenberger) and Cybernetics department of Mendeleyev University of Chemical Technology of Russia (MUCTR) (Prof. Dr. N. Menshutina) sponsored by Swiss National Science Foundation. This project has been started at 2001 and will be finished at the end of 2003.

The aim of project is to develop and implement modern learning and teaching technologies in field of pharmaceutics. This activity includes creation of multimedia study courses and their implementation with learning management system to archive goals of distant, convenient to students and teachers education facility. Another significant aim of this joint project is knowledge sharing between University of Basel and MUCTR which is done by translating course materials to bilingual Russian-German form. At MUCTR these multimedia lectures are hold for student of Faculty of Pharmaceutical Technology in Russian language and for students of Institute of Pharmaceutical Technology of University of Basel in German.

Since the beginning of this project there were following activities performed: 3 multimedia courses were developed in Institute of Pharmaceutical Technology in University of Basel. There are: "Solid dosage forms", "Semi-solid dosage forms" and "Liquid sterile dosage forms". These courses have been translated into Russian language by Cybernetics department of MUCTR and now are used for teaching students in faculty of Pharmaceutical Technology of MUCTR. With the help of URZ (Universität Rechen Zentrum, UniBasel) the PhysPharm software had been developed by Institute of Pharmaceutical Technology and translated to Russian by Cybernetics department of MUCTR. PhysPharm Russian Edition is available now for MUCTR students campus-wide. At Cybernetics department of MUCTR the multimedia course "Technology and equipment for pharmaceutical production, solid, semi-solid and liquid-sterile dosage forms" has been developed. This course is currently being evaluated and translated from Russian to English and German.

### Currently performing activities are:

1 Implementation of learning management system (LMS) in the Institute of Pharmaceutical Technology of University of Basel on the base of WebCT software with support of URZ. This LMS provides powerful capabilities for course content management, tracking student's activity and their progress. This helps students to have a clear view to the course "backbone" and guides them to better understanding the key points of theoretical and practical course materials. For MUCTR the Claroline software will be implemented as LMS. Claroline has the same basic features as WebCT and is distributed under the rules of General Public License.

2 Development Macromedia Flash-based test designing and exam-preparation software. Flash technology combines two main advantages among the existing packages: it could be easily integrated into any existing LMS and apply no technical restrictions for visualization of different aspects of the subject.

3 Starting from February 2003 the learning management system on the base of Claroline software will be opened.

The ongoing activity is translation of all lectures and supplement materials into English language. Further plans are involving creation of virtual lab training environment based on CLIPS expert system shell with a combination of artificial neuron network packages. These works are being developed at Basel and Moscow. As initial step of this feature work two textbooks have been issued:

1 "Information systems and databases for pharmaceutics" Authors: T. Mescheryakova, N. Menshutina, H. Leuenberger, S. Goncharova, Y. Mishina. (This textbook also has English edition)
2 "Multimedia courses for chemical technology and pharmaceutics". Edited by N.Menshutina and H. Leuenberger. (In print)

### H.4.1 Creation of expert system for galenical science

Second currently performing joint activity between MUCTR and Institute of Pharmaceutical Technology UniBasel is development of hybrid expert system for galenical science to distinguish between different dosage form manufacturing. In range of this activity there are teo PhD works (one at UniBasel, one at MUCTR) are currently running. At MUCTR the database of pharmaceutical excipients had been developed on the base of theoretical data provided by Institute of Pharmaceutical Technology, University of Basel.

### H.4.2 Freeze drying activity

Third currently performing joint activity between MUCTR and Institute of Pharmaceutical Technology (UniBasel) is mathematical modeling and studying of freeze drying process. This technology could find a wide range of application, in nanoscience, pharmaceutical technology and food industry. There are two PhD works are currently running at this topic, one in Basel and one at MUCTR.

## *H. 5. Research*

### H.5.1 General Remarks

It is a goal to intensify the research collaboration locally (Basel area) and nationally (Center of Pharmaceutical Sciences Basel-Zurich). A major focus in Basel will be the cooperation with the Basel NCCR Nanocenter in the area of novel drug delivery systems especially the preparation of nanocontainers (grant proposal to the Swiss National Science Foundation in collaboration with P. Hunziker, University Hospital, Ueli Aebi, Biocenter and Wolfgang Meier, Institute of Physical Chemistry) and the cooperation with the FHBB in the area of innovation chain management (Fachhochschule beider Basel). Another important focus is to intensify basic research to understand complex systems such as formulations. The research in complex systems (analysis, behavior) is not yet a megatrend in science [Proceedings CASS-Symposium 2000, M. Leuthold, H. Leuenberger, E.R. Weibel (Eds.)] but will soon become one parallel to

the progress in Bioinformatics and as the computers still improve the performance at an affordable prize. Thus, it is important that the new generation of students gets used to the application of artificial neural networks and percolation theory, statistical experimental design, and expert systems. In this respect the cooperation with the cybernetic department of MUCTR will be beneficial. (see international cooperation). Implementation of new cooperation projects within the existing network (China Pharmaceutical University, NanJing; Chinese National Human Genome Center, Beijing) in connection with the planned Swiss House in China. Specifically in the area of drug absorption, an embedding of our activities within the biophysics research of the University of Basel will be pursued, in particular in cooperation with the Biocenter department (Prof. Seelig).
Furthermore, cellular pharmacokinetics work will be broadened by combining our physical chemical expertise with the molecular biology approach on transporters of the Institute of Clinical Pharmacology of the University of Basel (Prof. J. Drewe).

The Research Expertise of the Institute of Pharmaceutical Technology takes advantage of its location in Basel as home of major as well as small and medium sized pharmaceutical enterprises, is complementary to the focus of its sister group at the ETH Zurich and can be summarized as follows:

**Research in Powder Technology:**

Dry and Moist Agglomeration of Powder, i.e. Granulation, Tabletting supported by the Swiss National Science Foundation; Control and Scale-up of the Moist Agglomeration Process.

**Application of Percolation Theory:**

Design of robust formulations; study the behavior of complex systems (binary, multicomponent) of solid and liquid dosage forms including problems related with the structure of water.

**Research for New Process Technologies:**

Vacuum fluidized bed and spray-freeze drying processes for the production of new drug delivery systems, semi-continuous processes to avoid scale-up, to improve quality and to implement a "Fast Time to Market Concept".

**Drug Delivery and Absorption:**

Major strength in this area results from the use of physicochemical and biophysical methodology combined with mathematical modeling to investigate phenomena taking place in biological material and applying to transepithelial and biomembrane drug transport. Topics of study are: passive and iontophoretic (trans)dermal transport, phospholipid bilayer permeation, bioavailability of topical formulations, permeation kinetics in Caco-2 cell monolayers. Focus is to develop unifying models for a mechanistic understanding of the involved phenomena.

**Research Policy**

Adapted to the local opportunities; problem oriented, derived from needs (applied and basic research);

themes, projects are interrelated; identification of interesting niche topics; optimization of return on investment; close cooperation with industry (pharma, equipment manufacturer).

## H.5.2 Publications 2002

A novel approach to the characterization of polar liquids Part 2: Hydrophilic Solutions. Publication, in english. Stengele Andrea, Rey Stephanie, Leuenberger Hans, Int.J.Pharm. 241 (2), 2002, 231-240. ISSN 0378-5173.

Creation of multimedia education courses in the pharmaceutics area. Proceedings, in english. Shishulin D.V., Menshutina Nathalia V., Avramenko G..A., Leuenberger Hans, Gordeev L.S. Proc.CHISA 2002 on CD 2002. 15th International Congress of Chemical and Process Engineering; Prague 25.08.02 - 29.08.02.

From Batch to Continuous Processes. A new trend in the Production of pharmaceutical granulates. Proceedings, in english. Werani Jürgen, Grünberg Mads, Ober Christian, Leuenberger Hans, Proceedings 4WCPT cd 2002. ISBN 085 825 7947. 4th World Congress on Particle Technology; Sydney 21.07.02 - 25.07.02.

Nanocomposite drug carriers for low water soluble drugs. Proceedings/Abstracts. Leuenberger Hans, 2002. 2002 PARTICLES; Orlando 20.04.02 - 23.04.02, p. 99.

Physikalische Pharmazie. Book, in german. Leuenberger Hans, Martin Physikalische Pharmazie 4.Aufl 2002. Editor(s); Leuenberger Hans, ISBN 3-8047-1722-5.

Powder - the fourth state of matter?. Publication, in japanese. Leuenberger Hans, Pharm.Technol.Jpn 18 (7), 2002, 995-1001. ISSN 0910-4739.

Rise and Fall of Megatrends in Science. Proceedings, in english. Proc.CASS-Symposium2000 2002, 1-126. Editor(s); Leuthold Margrit, Leuenberger Hans, Weibel Ewald R. ISBN 3-7965-1939-3. 2000 CASS-Event; Bern 30.11.00 - 01.12.00.

Scale-up in the 4th dimension in the field of granulation and drying or how to avoid classical scale-up. Publication, in english. IN PREPARATION. Leuenberger Hans, Powder Technol. 2002. ISSN 0032-5910.

Spray Freeze Drying - The Process of Choice for low water soluble Drugs?. Publication, in english. Leuenberger Hans, J.Nanop.Res. 4 (1.2), 2002, 111-119. ISSN 1388-0764.

D. Hummel and G. Imanidis. Structure of Multi-phasic Dermatological Formulations and the Influence of the Structure and of Vehicle Evaporation on Transdermal Drug Permeation. In: R. Marks, J-L. Leveque and R. Voegeli (Eds.), The Essential Stratum Corneum, Martin Dunitz, London, 2002, pp. 119-124.

C. Kochhar and G. Imanidis. Transdermal Iontophoresis of Leuprolide In Vitro under Constant Voltage and Constant Current Conditions: Physicochemical Modelling and the Effect of Adjuvants. In: R. Marks, J-L. Leveque and R. Voegeli (Eds.), The Essential Stratum Corneum, Martin Dunitz, London, 2002, pp. 149-155.

T. Schmidt, N. Widler, F. Gafner and G. Imanidis. Stratum Corneum Lipid Composition as a Predictive Tool for Permeability? In: R. Marks, J-L. Leveque and R. Voegeli (Eds.), The Essential Stratum Corneum, Martin Dunitz, London, 2002, pp. 169-174.

T. Tassopoulos, S. Maeder, G. Imanidis, V. Figueiredo, E.W. Smith and C. Surber. Evaluation of a Direct Spectrophotometric Method for Percutaneous Bioavailability Studies. In: R. Marks, J-L. Leveque and R. Voegeli (Eds.), The Essential Stratum Corneum, Martin Dunitz, London, 2002, pp. 175-178.

C. Kochhar and G. Imanidis. In Vitro Transdermal Iontophoretic Delivery of Leuprolide - Mechanisms under Constant Voltage Application. J. Pharm. Sci. 92:85-97 (2003).

B. Müller, M. Kasper, C. Surber and G. Imanidis. Permeation, Metabolism and Site of Action Concentration of Nicotinic Acid Derivatives in Human Skin - Correlation with Topical Pharmacological Effect. Eur. J. Pharm. Sci. submitted (2002).

C. Kochhar and G. Imanidis. In Vitro Transdermal Iontophoretic Delivery of Leuprolide under Constant Current Application. J. Pharm. Sci. submitted (2002).

Gabriele Betz, Pascale Junker Bürgin, Hans Leuenberger. Power consumption profile analysis and tensile strength measurements during moist agglomeration. Int. J. Pharm., in press.

Gabriele Betz, Pascale Junker Bürgin, Hans Leuenberger. Batch and Continuous Processing in the Production of Pharmaceutical Granules. Pharmaceutical Development and Technology, accepted.

## H.5.3 List of Presentations as an Invited Speaker, Participation in Symposia, Workshops, Project/coordination Meetings, Organisation of workshops etc.

| | | |
|---|---|---|
| 30.01.02 to 31.01.02, Binzen/Lörrach Leuenberger Hans | No.47 Technology Training Center (TTC)- Workshop | High shear processing |
| 5.3.02 to 7.3.02, Binzen/Lörrach Leuenberger Hans | No.49 Technology Training Center (TTC)- Workshop | Granulation & Tabletting |
| 8.4.02 to 11.4.02 Florence, Italy G. Betz | 4th World Meeting on Pharmaceutics Biopharmaceutics Pharmaceutical Technology | G. Betz, P. Junker Bürgin, H. Leuenberger, Power Consumption Profile Analysis and Tensile Strength Measurements during Moist Agglomeration |
| 9.4.02, Weimar Leuenberger Hans Chairman | GMP - Pharma Symposium Modernization of the Russian Pharmaceutical Industry | Satellite Symposium of the bilateral german-russian meeting „St.Petersburger Gespräche II“ between President Putin and Chancellor Schröder |
| 20.4.02 to 23.4.02, Orlando Leuenberger Hans | PARTICLES Medical/Biochemical Diagnostic, Pharmaceutical, and Drug Delivery Applications of Particle Technology | Nanocomposite drug carriers for low water soluble drugs |
| 22.5.02, Philadelphia Leuenberger Hans | Global Trends in pharmaceutical manufacturing containments & product handling systems. Symposium sponsored by Glatt Dresden. | Trends in Pharmaceutical Manufacturing - Challenges of the New Millennium |

| | | |
|---|---|---|
| 8.6.02 to 15.6.02, Beijing and Shanghai<br>Betz Gabriele on behalf of H.Leuenberger | Swiss Innovation Week Switzerland-China Scientific Workshop. Focus on Environment, Public Transport and Life Sciences. New Swiss Technologies and Findings for China | Research at the Institute of Pharmaceutical Technology, Pharmacenter, University of Basel. |
| 12.6.02, Albi CT Cedex<br>Invited participant of the Meeting.<br>Leuenberger Hans | Event at the École des Mines Albi-Carmaux. Conseil Scientifique de l'Ecole des Mines d'Albi-Carmaux. | |
| 27.6.02, Moscow<br>Leuenberger Hans | Invited Member of the board, participating at the PhD-Defense of M.Puchkov | |
| 21.7.02 to 25.7.02, Sydney<br>Leuenberger Hans | 4th World Congress on Particle Technology | Invited Lecture: From Batch to Continuous Processes. A new trend in the Production of pharmaceutical granulates |
| 25.8.02 to 27.8.02, Prague<br>Leuenberger Hans | CAETS Council Meeting and Symposium on Synergies of Engineering Branches. | |
| 3.9.02 to 6.9.02, Pontresina<br>Leuenberger Hans and Plitzko Matthias | NCCR Nanoscale Science Workshop | Manufacturing nano-composite particles by spray freeze drying at atmospheric pressure |
| 12.9.02, Albi CT Cedex<br>Leuenberger Hans | PhD-Defence meeting | Membre du jury de la thèse de Alexandre GIL |
| 18.10.02<br>Leuenberger Hans | CASS Klausurtagung, Liestal | |
| 21.10.02 to 23.10.02, Basel<br>Leuenberger Hans | PDA Central Europe Chapter Forum. Moist Heat Sterilization and PDA Technical Monograph No.1 | Physical Basis of Steam-Sterilization |
| 6.11.02 to 8.11.02 Ann Arbor, MI, USA<br>M. Sutter, T. Fiechter and G. Imanidis | Oral presentation at the Global Pharmaceutical Education Network Meeting GPEN2002 | Membrane Properties Affecting Drug Permeabilit |

| | | |
|---|---|---|
| 6.11.02 to 8.11.02<br>Ann Arbor,<br>MI, USA<br>G. Imanidis | Oral presentation at the Global Pharmaceutical Education Network Meeting GPEN2002 | The C* Approach |
| 6.11.02 to 8.11.02<br>Ann Arbor,<br>MI, USA<br>G. Imanidis | Oral presentation at the Global Pharmaceutical Education Network Meeting GPEN2002, Ann Arbor, MI, USA, November 6-8, 2002 | Insights Gained by Modeling Constant Voltage Iontophoresis |
| 3.12.02 to 5.12.02,<br>Binzen/Lörrach<br>Leuenberger Hans | No.58 Technology Training Center (TTC)- Workshop | Pellet Workshop |
| 6.12.02<br>Basel<br>Leuenberger Hans<br>Eichler Klaus | „Das Narrenschiff 2002"<br>Event organized in collaboration with the cogito foundation, 8832 Wollerau, www.cogitofoundation.ch | Homage for Sebastian Brant and promotion of transdisciplinary collaboration beyond the structural borders of the university |

## H.5.4 List of PhD-Thesises in Pharmaceutical Technology completed in 2002

| **PhD student** | | **Title** | **Funding/Location** |
|---|---|---|---|
| Bongartz | Christian | Modifying Surface Properties of Crystalline Drug Substances by Addition of Surface Active Substances During the Final Crystallization | F. Hoffmann - La Roche AG, Basel |
| Stengele | Andrea | Ein Beitrag zur Charakterisierung von binären, wässrigen Lösungsmittelmischungen mittels dielektrischer Spektroskopie | Institute of Pharmaceutical Technology, University of Basel. |
| Ketani | Damla | Ein Beitrag zur Theorie von hydrophilen Lösungen | Institute of Pharmaceutical Technology, University of Basel. |
| Matschke | Christian | Slow release of veterinary formulations | Novartis Animal Health AG, Basel |
| Schmid | Timo | β-adrenerge Substanzen für eine transdermale Applikation: Modelle zur Vorhersage der Permeabilität | Mepha Ltd.<br>Thesis mentor:<br>PD Dr. G.Imanidis |

# I. Outlook 2003

## *I. 1. On-Going Research Activities*

### I.1.1 PhD-Students

| **PhD Student** | | **Topic (Working Title)** | **Funding and Location** |
|---|---|---|---|
| Altenbach | Melanie | Einfluss der Molekülladung und der Molekülliphophilie auf den transdermalen iontophoretischen Transport durch die menschliche Epidermis | Institute of Pharmaceutical Technology, University of Basel. |
| Bausch | Ursula | Steriles Abfüllen von Lösungen mit Zellen und Proteinen | Alphacos SA, CH 2822 Courroux; Institute of Pharmaceutical Technology, University of Basel |
| Faatz | Susan | Ländervergleich Irland-Schweiz betreffend der Rahmenbedingungen für die Pharmazeutische Industrie | Private source, in Collaboration with Prof. B. Hotz-Hart, BBT, Bern and the University of Zürich |
| Fueg | Lise-Marie | Einblick in die Entwicklung von Pulvern zur Inhalation mit dem SkyePharma multidose Dry Powder Inhaler (mDPI) | Skye Pharma AG, Muttenz |
| Guntermann | Anja | Scale-up of tablet formulations using the Presster TM equipment | Pfizer GmbH, Arzneimittelwerk Gödecke, Freiburg i.Br.; Institute of Pharmaceutical Technology, Industrial Pharmacy Lab, Basel |
| Hernandez | Engracia Maria | Dielectric Spectroscopy of hydrophilic solutions | Institute of Pharmaceutical Technology, University of Basel |
| Krabichler | Michaela | The preventive effect of α-tocopherol on UVA/B photodamage in human skin fibroblasts | F. Hoffmann - La Roche AG, Basel; Institute of Pharmaceutical Technology, Basel (part time) |
| Kuny | Tanja | Kompressionsverhalten von Enzymen am Beispiel der Laktase | Institute of Pharmaceutical Technology, University of Basel |
| Lanz | Michael | The behaviour of disordered particulate systems in case of dry and moist agglomeration processes | Swiss National Science Foundation, Bern, Grant No 20-58941.99; Institute of Pharmaceutical Technology; Basel |

| | | | |
|---|---|---|---|
| Lenz | Corinna | Suche nach kritischen Konzentrationen bei der Herstellung von Pellets in der Rotorwirbelschicht | Spirig AG, Egerkingen |
| Nalenz | Heiko | Einfluss der Struktur mehrphasiger topischer Formulierungen auf die Absorption | Institute of Pharmaceutical Technology, University of Basel |
| Plitzko | Mathias | The production of nanocomposites using the spray-freeze-drying technique | NCCR (National Center of Competence in Research) Nano-Center, Basel; Glatt GmbH Binzen Institute of Pharmaceutical Technology, University of Basel |
| Reitbauer | Susanne | Absorption pathways of drugs through Caco-2 cells | Institute of Pharmaceutical Technology, University of Basel |
| Russell-Gohmert | Frauke | On-line NIR project solid dosage forms | F. Hoffmann -La Roche AG, Basel |
| Sautter | Caroline | Slow release of veterinary formulations | Novartis Animal Health AG, Basel |
| Schiffmann | Axel | CIP-Systeme bei der Wirbelschicht Granulierung | Glatt GmbH, Binzen, D |
| Sukowski | Lars | Online Near-Infrared Spectroscopy: Noninvasive Determination of Residual Moisture in Entire Batches of Lyophilized Pharmaceutical Products | F. Hoffmann - La Roche AG, Basel |
| Sutter | Marc | The Influence of Phospholipid Bilayer Properties on Transmembrane Permeability | Institute of Pharmaceutical Technology, University of Basel |
| Tassopoulos | Tatjana | Evaluation of topical bioavailability of MBC in human stratum corneum by tape stripping using a direct spectroscopic method | Institute of Hospital Pharmacy, University Hospital Basel |
| Von Orelli | Johannes | Development of an expert system for solid dosage forms | Institute of Pharmaceutical Technology, University of Basel |
| Walter-de Rooy | Marijke | Konzeption, Entwicklung und Realisierung eines vernetzten e-Lehr-und-Lernprogrammes der Pharm.Technologie | Private sources; Institute of Pharmaceutical Technology, University of Basel (part time) |

## I.1.2 Postdoctoral Positions

| | | | |
|---|---|---|---|
| Dr. Betz | Gabriele | Implementation of Research and Teaching in the Industrial Pharmacy Laboratory Mülhauserstrasse 49/51 | Institute of Pharmaceutical Technology, University of Basel. |
| Tanaka | Hiroshi | Project work (2002) at the Industrial Pharmacy Laboratory | On sabbatical leave from Shionogi Co. & Ltd., Osaka, Japan |
| Dr. Puchkov | Maxim | New Learning and Teaching Technologies and expert systems, Industrial Pharmacy Laboratory | IT specialist for Expert Systems and Computational Science. On leave from MUCTR (cooperation project). |

## *I. 2. Grants and Operating Budget*

### I.2.1 Contribution of the University (figures 2001 costs - 2002 budget):

| | | | | |
|---|---|---|---|---|
| 2001 | (running costs): | CHF | 114 084 | |
| | (investment in equipment): | CHF | 153 865 | (incl.CHF 20 000 for PCs) |
| 2002 | Budget: | CHF | 98 500 | |
| | | CHF | 119 904 | (incl. CHF 26 300 for PCs) |

### I.2.2 External funding administered by the University

External funding administered by the University incl. Swiss National Science Foundation (SNF): CHF 169 339 (2001).

### I.2.3 Other third party money not administered by the University

Direct payments to PhD students (individ. and SNF salaries): **CHF 360 000 (estimate)**

New Equipment sponsored by Pfizer (2001): Presster (the first in Europe!) equipment for the PhD topic of Anja Guntermann, Industrial Pharmacy Lab (Technology Center) in connection with the scale-up of tabletting process: **CHF 750 000**

Capsule filler donated by Pfizer 2001 Industrial Pharmacy Lab (Technology Center):

CHF not estimated → **new price > CHF 100 000**

Laboratory equipment incl. glassware, drugs and excipients for technical use in the practical training labs of the Institute of Pharmaceutical Technology sponsored by the Pharmaceutical Industry: total estimated value **CHF 50 000**

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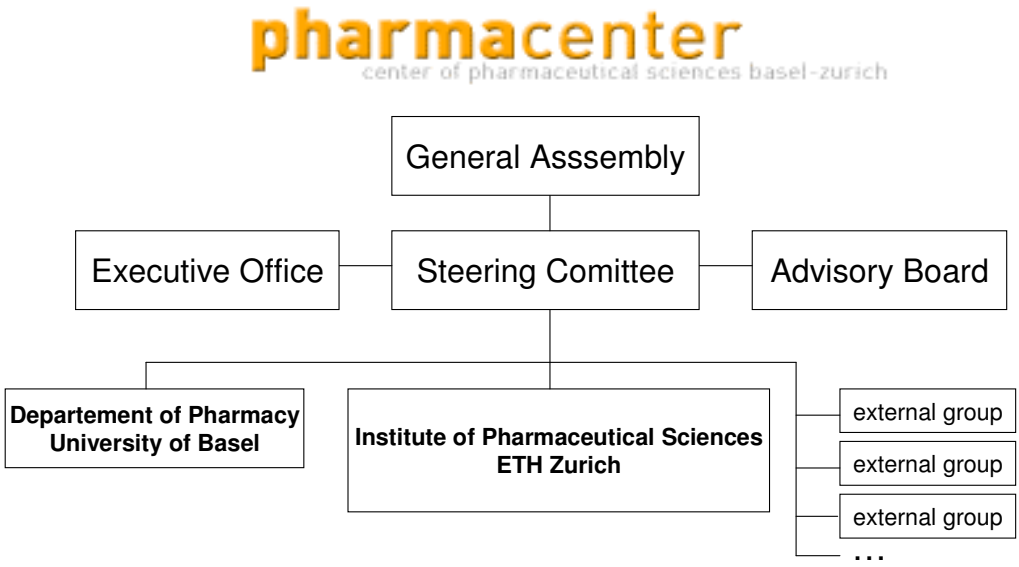
**Total sum: > CHF 1 260 000**

## J. Organization charts




**Organisation**

**www.pharmacenter.ch**

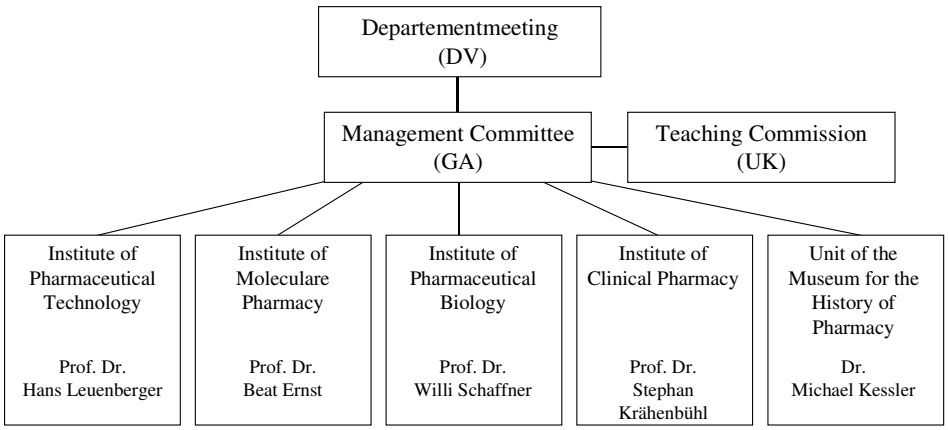
### Steering Committee Members 2001

- G. Folkers, President
- H. Wunderli (ETH)
- H.Leuenberger
- A.Eberle (external groups)

### Executive Office

- H.P.Wessels, Managing Director

# ORGANISATION
# DEPARTMENT of PHARMACY



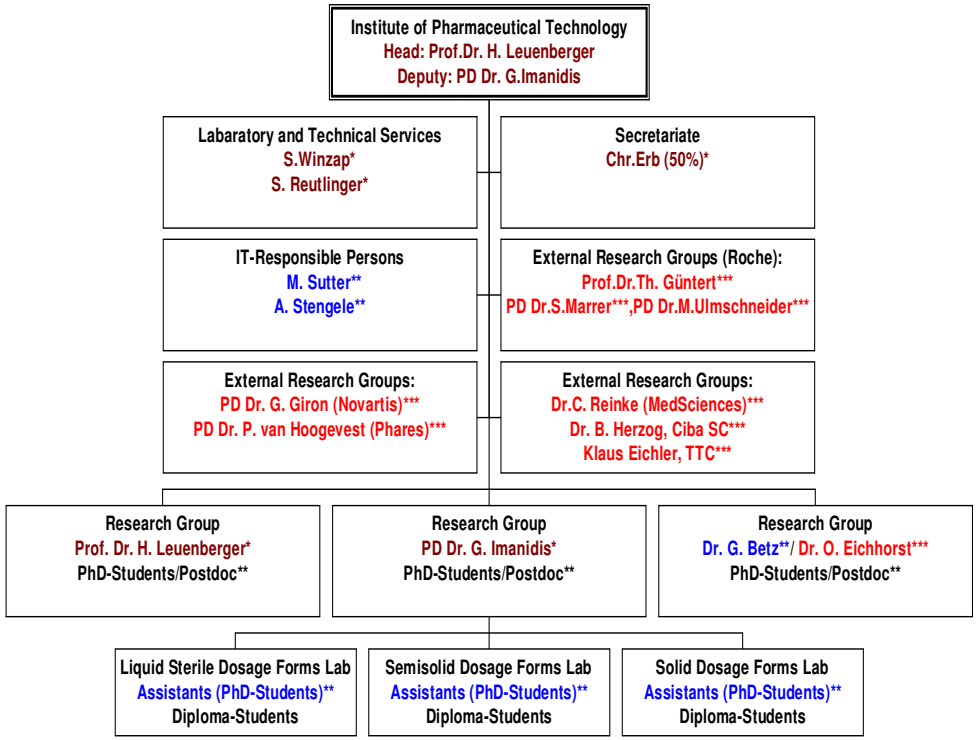

## Management Committee 2001

- H. Leuenberger (Vorsitz),
- B. Ernst
- W. Schaffner
- J. Krähenbühl

## Teaching Commission

- B. Ernst (Vorsitz)

# *Organisation; Institute of Pharm.Tech.*




***Employees of the University**

****PhD/Postdoc students**
**(non permanent positions, support by University, SNF, private grants etc.)**

*****External docents**
**(not employees of the University)**

# K. Reports / Contributions from External Docents

## *K. 1. PD Dr. D. Giron*

### K.1.1 Activities

### Symposium organization/scientific committee

- PhandTA6 (Pharmacy and Thermal Analysis), 26-30 May 2002, Ascona
- Als Präsidentin der STK: Tagung in Greifensee, 6 November, 2002
- 16-18.12.02, Lyon, Colloque: Polymorphisme et Morphologie. De la cristallisation au produit formulé.

### Lectures

| | | |
|---|---|---|
| 26.05.02 | PhandTA 6 (Pharmacy and Thermal Analysis), Ascona | "Characterization of Salts of Drug Substance", |
| 28.05.02 | PhandTA 6 (Pharmacy and Thermal Analysis), Ascona | S. Garnier, M. Mutz and D. Giron, "The use of organic vapour atmospheres to quantify amorphous content in pharmaceutical substances by isothermal calorimetry" |
| 10.09.02 | Plenary Lecture, 15th International Symposium on Industrial Crystallisation, ISIC15, Sorrento | "Monitoring of polymorphism, from detection to quantification", |
| 17.12.02 | Colloque: Polymorphisme et Morphologie. De la cristallisation au produit formulé, Lyon | "Application des méthodes thermiques et calorimètriques pour la caractérisation de l'état solide dans le développement pharmaceutique". |

### Workshops, lectures at university

| | | |
|---|---|---|
| 13.05.02 | Pharmaceutical University of Nancy | Méthodes analytiques de pureté |
| | Wahlpraktikum; Pharmaceutical Institut Basel | "Thermische Analyse" |
| 12.12.02 | Chemical and Physical Institut Lyon, Formation continue | Analyse thermique appliquée à la pharmacie |

### K.1.2 Dissertation

First opponent for the dissertation of Aukrust, Audun, *"Physicochemical Characterization of Crystal Forms of some Organic Metal Complexes Used in Magnetic Resonance Imaging"*. Prof. L.K. Sydnes, Department of Chemistry University of Bergen, 14.10.2002.

### K.1.3 Publications

- D.Giron and D.J.W. Grant, Chapter 3, "*Evaluation of solid state properties of salts*", IUPAC Monograph "Pharmaceutical Salt Selection" H. Stahl and C. Wermuth Eds, Helvetica Chim.Acta, March 2002
- D. Giron, Chapter *"Thermal Analysis of Drugs and Drug Products"*, Encyclopedia of Pharmaceutical Technology, J.Swarbrick and J.C. Boylan eds, Marcel Dekker, p.2766-2793, May 2002
- D. Giron, *"Applications of thermal analysis and coupled techniques in pharmaceutical industry",* J. Therm. Anal. Cal., 68, 2002, 335-357.
- D. Giron, C. Goldbronn, M. Mutz, S. Pfeffer, P. Piechon and P. Schwab, *"Solid state characterizations of pharmaceutical hydrates"*, J. Therm. Anal. Cal., 68, 2002, 453-465.
- E.Tedesco, L.Viola, S.Pfeffer and D. Giron, *"Crystal structure elucidation and morphology study of pharmaceuticals in development",* CrystEngComm, 2002, 4, 1-8.
- D. Giron, "Monitoring of polymorphism, from detection to quantification", procedures ISIC15, 2002.

#### Posters

- D. Giron, M. Mutz, STK Tagung in Greifensee, Nov. 2002
- "*Use of Thermal Analysis Techniques for Polymeric Excipients. Some Examples*"
- D. Giron, S. Pfeffer, P. Piechon, PhandTA, Ascona and STK Tagung in Greifensee
- "*Efficient use of TG-MS Coupled Technique in Pharmaceutical Development*"
- M. van Bruijnsvoort, C. Hartmann, D. Giron and P. Kiechle, *"Application of CE in the pharmaceutical industry", HPCE2002, Stockholm*

#### Scientific nomination at Novartis in 2002

Principal fellow

## *K. 2. T.W. Guentert*

In addition to the lectures in Biopharmaceutics, Drug Metabolism and Instrumental Analysis, extensive restructuring took place to achieve a higher degree of coordination within the Pharmacy curriculum.

## K.2.1 List of Dissertations, Publications, Talks/Posters

### Dissertations

### Ongoing Dissertations:

- Susan Grange, University Basel Pharmacokinetic-pharmacodynamic modeling as a tool to extrapolate dose-effect relationships from animal to man. (Beginning 1996)
- Stefanie Lerch, University Bern Ifosfamidtherapie assoziierte Enzephalopathie und ihre Interaktion mit Benzodiazepinrezeptoren (Beginning 2000)
- Olivier Luttringer, University Basel Physiologically-based Modeling of Active Transport Processes. (Beginning 2000)
- Shiva Neysari, University Basel Characterization of the functional coupling and binding mode of Neuropeptide-Tyrosine (NPY) Y2 and Y5 receptors: Implications for their functional role (Beginning 2000)

### Publications / Abstracts

- O. Luttringer, F.-P. Theil, T. Lavé, K. Wernli-Kuratli, T.W. Guentert, A. de Saizieu: Influence of isolation procedure, extracellular matrix and dexamethasone on the regulation of membrane transporters gene expression in rat hepatocytes. Biochem. Pharmacol. 7434, 1-14, 2002.
- F.-P. Theil, T.W. Guentert, S. Haddad, P. Poulin: Utility of physiologically based pharmacokinetic models to drug development and rational drug discovery candidate selection. Toxicology Letters 00 1-21, 2002
- Symposium: Clinical SignificanceC. Funk, M. Pantze, S. Haddad, J. Huwyler, M. of Drug Transporting Proteins,Schmitt, T. Guentert: Basel, SwitzerlandImportance of drug transporting proteins for drug 2002, March 22 development.

## K.2.2 Invited Speaker

| | | |
|---|---|---|
| 18 – 20 June, 2002 | 29th Annual Meeting of the Predictive Models in Early Risk Assessment of Japanese Society of ToxicologyNovel Drug Candidates. Negoya, Japan | |
| 20-23 October, 2002 | EUFEPS 2002 Developability Integrated in Early Drug 7th European Congress of Development. | Pharmaceutical SciencesAbstract: Europ. J. Pharm. Sci 17S, S1 (2002) Stockholm, Sweden |
| 9. – 11. December 2002 | EUFEPS 2002 Reengineering of Drug Development (Workshop) 10th European Conference Basel, Switzerland | |

### K.2.3 External Courses

- Faculty Member in Workshop in Basic Pharmacokinetics, Dept. of Pharmacy, Univ. Manchester: ManchesterJuly, 14 – 19, 2002

### K.2.4 Research 2002

- -In vitro absorption models
- -Influence of galenical factors on drug absorption
- -Prediction of drug behavior in humans based on animal and in vitro data
  Simulation techniques
  Pharmacogenomics

## *K. 3. Dr. Bernd Herzog*

Ciba Specialty Chemicals G-9001.2.28

PO Box 1266

D-79630 Grenzach-Wyhlen

### K.3.1 Betreuung von Lehrveranstaltungen in 2002

- Es wurden zwei Seminargruppen im Galenik-Seminar betreut mit den Themen:
  Sonnenschutz – Grundlagen und
  Sonnenschutz - Anwendunegn.

### K.3.2 Publikationen und Vorträge in 2002

- "Prediction of Sun Protection Factors by Calculation of Transmissions with a Calibrated Step Film Model", Bernd Herzog, J. Cosmet. Sci. 53 (2002) 11 – 26
- "In vivo and in vitro assessment of UVA protection by sunscreen formulations containing either butyl methoxy dibenzoyl methane, methylene bis-benzotriazolyl tetramethylbutylphenol, or microfine ZnO", B. Herzog, S. Mongiat, C. Deshayes, M. Neuhaus, K. Sommer and A. Mantler, Int. J. Cosmet. Sci. 24 (2002) 170 – 185
- "Prediction of Sun Protection Factors by Calculation of Transmissions with a Calibrated Step Film Model", Bernd Herzog, 4th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Florence, Italy, 8th to 11th April 2002 (poster)
- "Overview of New UV-Filters with Special Reference to Children (Safety Aspects)", Uli Osterwlder and Bernd Herzog, 25th Symposium of the Belgian Association of Dermato-Cosmetic Sciences (BADECOS), Brussels, 20th April 2002 (oral presentation)
- "Sun Protection beyond the Sun Protection Factor – New Efficient UVA/Broadband Filters", Uli Osterwalder and Bernd Herzog, 20th World Congress of Dermatology, Paris, 1st to 5th July 2002 (poster)
- "Novel Chemistry in Photoprotection – Benzotriazol and Hydroxyphenyltriazine", Uli Osterwalder, Bernd Herzog, Dietmar Hüglin, American Society for Photobiology, Quebec, Canada, July 13 – 17, 2002 (oral presentation)

- "Sun Protection beyond Erythema Prevention – Day Care Formulas with Broadband Filters Are more Efficient in Reducing UVA Induced Skin Damage", W. Baschong, S. Mongiat, B. Herzog, C. Artmann, I Congresso Latino americano de Fotobiología, Lima/Perú, 28th August – 1st September 2002 (poster)
- "UV Protection beyond Erythema Prevention – the Need for Novel Broad Spectrum UVB/UVA Sun Filters", Werner Baschong, Bernd Herzog and Uli Osterwalder, I Congresso Latino americano de Fotobiología, Lima/Perú, 28th August – 1st September 2002 (oral presentation)
- "Particle Charcterization", Bernd Herzog, Polymer Network Meeting, Grenzach, 18th Sept. 2002 (oral presentation)
- 10. "Hydroxyphenyltriazines: A new generation of cosmetic UV filters with superior photoprotection", D. Hueglin, B. Herzog, S. Mongiat, 22nd IFSCC Congress, 2002, Edinburgh (oral presenation)
- "In vivo and in vitro assessment of UVA protection by sunscreen formulations containing either ZnO, butyl methoxy dibenzoyl methane, methylene bis-benzotriazolyl tetramethylbutylphenol, or bis-ethylhexyloxyphenol methoxyphenyl triazine", B. Herzog, S. Mongiat, C. Deshayes, M. Neuhaus, K. Quass, A. Mantler, C. Comte, 22nd IFSCC Congress, 2002, Edinburgh (oral presentation)
- "Zum Sonnenschutz der Haut: Neue Entwicklungen bei UV-Absorbern und Messmethoden", B. Herzog, Universität Potsdam, Seminar Prof. H.-G. Löhmannsröben, 12th Nov. 2002 )oral presentation)
- "New Systems of Broad-Spectrum UV Protection", Uli Osterwalder and Bernd Herzog, IFSCC Magazine 5 (2002), No. 3, 169 – 175
- "Sun Protection Factors and UVA-Parameters of O/W Sunscreen Emulsions Containing Bis-Ethylhexyloxy Methoxyphenyl Triazine", Bernd Herzog, Cyrille Deshayes, Katja Quass, Sébastien Mongiat, www.ip.com, PCOM000008768D, 11th July 2002

## *K. 4. PD Dr. Peter van Hoogevest*

### K.4.1 Publication

- Leigh M., van Hoogevest P., Tiemessen H., Optimisng the oral bioavailability of the poorly water-soluble drug cyclosporin A using membrane lipid technology in: Drug Delivery systems& sciences 2001, vol 1, no 3, pp 73-77

## *K. 5. PD Dr.Stephan Marrer*

### K.5.1 Publications

Excipients´ Functionality Impact on Product Quality and Process Performance. Publication, in english. Stephan Marrer, Heribert Häusler, Pharm. Ind 64 (10), 1083 - 1086, 2002.

## K.5.2 Contributions to research and teaching

- PD Stephan Marrer, PhD, responsible for Galenical Bulk Operations at Roche is teaching Quality Assurance topics.
- PD Michel Ulmschneider, PhD, is private docent at the Université de Haute Alsace, Mulhouse and is supervising with PD Dr.S.Marrer for the PhD thesis of Lars Sukowski at Roche (see K.5.3)

## K.5.3 On-Going Research Activities

### PhD-Students, Topics (working title), Supported by

| | | | |
|---|---|---|---|
| Sukowski | Lars | Noninvasive Determination of Residual Moisture in Entire Batches of Lyophilized Pharmaceutical Products (working title) | F.Hoffmann - La Roche AG |
| Russell | Frauke | Near-Infrared Transmission Spectroscopy - a fast and non-destructive method for dissolution testing of solid dosage forms | F.Hoffmann - La Roche AG |

## K.5.4 Cooperation with Industry

Frau Ursula Bausch/F.Hoffmann-La Roche AG. Behaviour of proteins during galenical manufacturing (filling operations); considerations to treat proteins with care.

# *K. 6. Dr. Claudia Reinke*

## K.6.1 Investigation of the influence of antioxidative vitamins (vitamin E and C) on UV-irradiated human skin fibroblasts

UV-B is a known carcinogen, because DNA absorbs radiation in this part of the wavelengthspectrum through formation of pyrimidine dimers. Further damage is being created by free radicals which cause the oxidation of proteins, membrane lipids and DNA. The amount of cellular damage determines if the cell will be repaired or is being eliminated via apoptosis.

To investigate the influence of antioxidative vitamins on UV-B-irradiated cells selected parameters are being taken into consideration. An important parameter is the DNA-repair rate of UV-damaged cells and the possible protective effect of antioxidative vitamins. For these investigations an ELISA-based antibody-labeling-technique is being used.

Another parameter is the measurement of the extent of cytotoxicity of radiation and the protective effect of antioxidative vitamins on the rate of apoptosis. Apoptosis is being measured via nick-end-labeling of DNA-strandbreaks that develop during DNA-degradation.

Further we investigate the tumor suppressor protein p53 which plays a keyrole between DNA-repair and apoptosis. P53 accumulates in the cellcore after cellular damage. It transcriptionally activates certain proteins which leads to cellcyclearrest in the G1-phase until complete repair of the damage. If the amount of damage is too high then p53 is responsible for the activation of the apoptosis-pathway to guarantee genomic stability. Therefore the influence of antioxidative vitamins on the p53-expression of UV-irradiated cells was of considerable interest for our work. For the quantification of p53 an ELISA is being used.

Preliminary results show that antioxidants such as vitamin E and C may probably be able to protect skin cells from the damaging effects of UV-radiation by enhancing the DNA repair rate.

## ACKNOWLEDGEMENTS

All the persons especially the external docents and the companies/institutions, who have supported research and teaching at the Institute of Pharmaceutical Technology are officially acknowledged.

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Basel, 18.2.2003 gez. Prof. Dr. H. Leuenberger