# SWISS PHARMA

Pharmakologie
Urologie
Mass Spectrometry
Right, First Time
Concept and Workflow

Swiss Journal of the Pharmaceutical Industry

Schweizerische Zeitschrift für die pharmazeutische Industrie

Revue suisse pour l'industrie pharmaceutique

Rivista svizzera per l'industria farmaceutica

3/13

# Orthopädie – Traumatologie – Chirurgie – Arthroskopie – Sportmedizin

## SWISS MED 1/11 (208 Seiten) Gespräche/Beiträge in SWISS MED aus den Jahren 1979 bis 2010

CHF 80.– + MWSt. (Schweiz) + Versandkosten

**Editorial**
Prof. Dr. med. André Gächter
Facharzt für Orthopädische Chirurgie und Traumatologie des Bewegungsapparates
Berit Klinik, 9052 Niederteufen (Schweiz)

Zitat aus dem Editorial:
«In diesem Erfahrungsschatz (SWISS MED 1/11; Red.) finden sich so viele Beiträge von prägenden ‹Grössen›, auch von umstrittenen Persönlichkeiten oder Weggefährten, die ohne ein grosses Aufheben davon zu machen bedeutende Weichen gestellt haben: Eine wichtige Fundgrube für alle, die sich für die Entwicklung der Orthopädie und Chirurgie – sowie deren Unterspezialitäten – interessieren.»

**Gespräche / Beiträge**
Auf mehr als 200 Seiten findet die Leserin/der Leser eine Kompilation der in SWISS MED seit der Gründung der Zeitschrift im Jahre 1979 bis und mit 2010 veröffentlichten Live-Interviews mit den damals aktiven Persönlichkeiten.

Zitat aus dem Editorial:
«Wir finden auch Perlen von Interviews und Beiträgen in dieser Ausgabe von SWISS MED (1/11; Red.) zu Themen wie der Entwicklung der Osteosynthese, der Arthroskopie, der Thromboseprophylaxe, der Technischen Orthopädie und Sportmedizin an den verschiedenen Kliniken von Fribourg bis nach St.Gallen.»

**Verlag Dr. Felix Wüst AG**
In der Hinterzelg 4
CH-8700 Küsnacht ZH
Telefax ++41 44 918 29 70
E-Mail felixwuest@bluewin.ch

# PERINATAL PHARMACOLOGY PERINATALE PHARMAKOLOGIE

SWISS MED 1/13
Swiss Association of Perinatal Pharmacology (SAPP)
5th Anniversary Meeting
Zurich, 29th November 2012

**PROCEEDINGS**

Gender specificity in (perinatal) pharmacology
Geschlechterunterschiede in der (perinatalen) Pharmakologie
– Prof. Dr. pharm. Ursula von Mandach, President SAPP, Zurich University Hospital, Zurich (Editorial)

Roots of perinatal pharmacoloy
– PD Dr. med. Béatrice Krauer-Mayer, Basel (Introduction)
– Prof. em. Frank E. Hytten, PhD, MD, FRCOG, Buckinghamshire, UK

Geschlechterunterschiede in der perinatalen Pharmakologie
Zusammenfassung weiterer Vorträge
– Wirkung von Drogen und Umweltchemikalien auf die sexuelle Differenzierung des Gehirns
  • Prof. Dr. med. Walter Lichtensteiger, Zürich
– Geschlechterspezifische Unterschiede beim Neugeborenen
  • Prof. Dr. med. Hans Ulrich Bucher, Zürich
– Geschlechterspezifische Beckenbodenerkrankungen
  • PD Dr. med. Verena Geissbühler, Winterthur
– Regulatorische Behörden und Geschlechter
  • Dr. med. Margaretha Bindschedler, Spiez

Gender specificity in (perinatal) pharmacology
Poster Abstracts
– Summaries drawn up by Dr. sc. nat. Barbara Lardi-Studler, Uster

PD Dr. med. Béatrice Krauer-Mayer
Erstes Ehrenmitglied der Schweizerischen Arbeitsgemeinschaft für Perinatale Pharmakologie (SAPP)
– Prof. Dr. pharm. Ursula von Mandach, Zürich

**SWISS MED 1/13**
**Perinatal Pharmacology/Perinatale Pharmakologie**
CHF 50.– pro Expl., exkl. MwSt. (Schweiz) und zuzüglich Versandkosten.

**Verlag Dr. Felix Wüst AG, In der Hinterzelg 4, CH-8700 Küsnacht, Telefax 0041 (0)44 918 29 70, E-Mail: felixwuest@bluewin.ch**

Swiss Journal of
the Pharmaceutical Industry

Schweizerische Zeitschrift
für die pharmazeutische Industrie

Revue suisse pour l'industrie
pharmaceutique

Rivista svizzera per l'industria
farmaceutica

SWISS PHARMA

SWISS PHARMA 35 (2013) Nr. 3

3/13

# INHALT

**IMPRESSUM** *2*

**RIGHT, FIRST TIME CONCEPT WORKFLOW** *3*

Right, First Time Concept and Workflow. A Paradigm Shift for a Smart & Lean *Six-sigma* Development
– *Prof. Dr. Hans Leuenberger, Pfeffingen BL*
– *Dr. Maxim Puchkov, Pfeffingen BL*
– *Dr. Bernhard Schneider, Muttenz BL*

**NEWS** *18*

Pharmatrans Sanaq AG/IFIIP GmbH: 9TH Scientific & Technical Forum 2013
Right, First Time Concept & Workflow to reduce Time to Market – Boosting Lean *Six-sigma* Quality Development

Pharmazeutische Mikrobiologie: Qualitätssicherung – Monitoring – Betriebshygiene

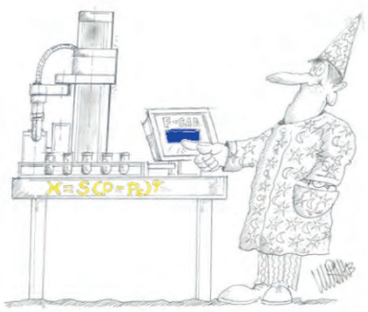
**PHARMAKOLOGIE UROLOGIE** *19*

Pharmakologie und Urologie
– *Prof. em. Dr. med. Dieter Hauri, Küsnacht ZH*

**MASS SPECTROMETRY** *23*

Belladonna Puzzle – An Application of Mass Spectrometry
– *Carina Lämmle, Dr. Rudolf Binder, Bad Saulgau (D)*

# TITELBILD



## Impressum

**Verlag, Abonnemente, Anzeigen:**
Verlag Dr. Felix Wüst AG
In der Hinterzelg 4 • CH-8700 Küsnacht ZH
Telefon 0041 (0)44 918 27 27 • Telefax 0041 (0)44 918 29 70
E-Mail: felixwuest@bluewin.ch

**Redaktion:**
**a) Allgemeiner Teil:** Dr. rer. publ. Felix Wüst
**b) Wissenschaftlicher Teil:**
Schweizerische Gesellschaft der Pharmazeutischen Wissenschaften (SGPhW)
Prof. Dr. Dr. h.c. mult. Hans Leuenberger, Institut für industrielle Pharmazie, Ifiip GmbH, Kreuzackerweg 12, CH-4148 Pfeffingen, hans.leuenberger@ifiip.ch, www.ifiip.ch





**Im Verlag Dr. Felix Wüst AG erscheinende Zeitschriften**

**Bestellung von Einzelheften**
Preis pro Exemplar in der Regel CHF 50.– exkl. MwSt. und zuzügliche Versandkosten. Bei grösseren Ausgaben gilt der Preis auf Anfrage bzw. gemäss Angebot.

**Als abonnierte Zeitschrift erscheinender Titel**
**Auch als Sonderheft (für Firmen, Verbände, Institutionen usw.) möglich**

**Swiss Pharma** — Schweizerische Zeitschrift für die pharmazeutische Industrie
ISSN 0251-1673 — Revue suisse pour l'industrie pharmaceutique
Rivista svizzera per l'industria farmaceutica

**Abonnemente für SWISS PHARMA**

CHF 290.– + Versandkosten

Schweiz: CHF 40.–
Europa: CHF 60.–
Airmail: CHF 200.–

**In unregelmässigen Abständen als Sonderhefte**
**(für Firmen, Verbände usw.) aufgelegte Titel (keine Abonnemente)**

Die hiernach aufgeführten Zeitschriften sind keine Periodika; sie können demnach nicht abonniert werden. Die einzelnen Ausgaben erscheinen in unregelmässigen Abständen im Auftrag von Firmen, Verbänden, Institutionen («Corporate Publishing») oder als Spezialausgaben des Verlags im Vorfeld besonderer Veranstaltungen.

**Swiss Biotech** — Schweizerische Zeitschrift für Biotechnologie
ISSN 0253-9675 — Revue suisse de biotechnologie
Rivista svizzera di biotecnologia

**Swiss Med** — Schweizerische Zeitschrift für Medizin und medizinische Technik
ISSN 0251-1665 — Revue suisse de médecine et de technique médicale
Rivista svizzera di medicina e tecnica medica

**Swiss Dent** — Schweizerische Zeitschrift für orale Präventiv- und Kurativmedizin
ISSN 0251-1657 — Revue suisse d'Odontostomatologie préventive et thérapeutique
Rivista svizzera di Odontologia e Stomatologia preventiva terapeutica

**Swiss Vet** — Schweizerische Zeitschrift für Veterinärmedizin
ISSN 0254-6337 — Revue suisse de médecine vétérinaire
Rivista svizzera di medicina veterinaria

**Swiss Food** — Schweizerische Zeitschrift für die Nahrungsmittelindustrie
ISSN 0251-1687 — Revue suisse pour l'industrie alimentaire
Rivista svizzera per l'industria alimentare

**Swiss Chem** — Schweizerische Zeitschrift für die chemische Industrie
ISSN 0251-1703 — Revue suisse pour l'industrie chimique
Rivista svizzera per l'industria chimica

**Swiss Materials** — Schweizerische Zeitschrift für Materialwissenschaft und Technologie
ISSN 1013-4476 — Revue suisse pour la science et la technologie des matériaux0
Rivista svizzera per la scienza e la tecnologia dei materiali

**Prepress und Druck**

Bubenberg Druck- und Verlags-AG • Monbijoustrasse 61 • Postfach • CH-3001 Bern
E-Mail: wuest@bubenberg.ch

# Right, First Time Concept and Workflow

## A Paradigm Shift for a Smart & Lean *Six-sigma* Development

Hans Leuenberger*[1, 2, 3], Maxim Puchkov[1, 3], Bernhard Schneider[4]

[1]Division of Pharmaceutical Technology, Department of Pharmaceutical Sciences, University of Basel, Klingelbergstrasse 50, CH-4056, Basel, Switzerland, www.pharma.unibas.ch
E-mail address: hans.leuenberger@unibas.ch, maxim.puchkov@unibas.ch,
[2]IFIIP GmbH, Institute for Innovation in Industrial Pharmacy; Kreuzackerweg 12, CH-4148 Pfeffingen, www.ifiip.ch
E-mail address: hans.leuenberger@ifiip.ch
[3]CINCAP GmbH; Kreuzackerweg 12, CH-4148 Pfeffingen, Switzerland, www.cincap.ch
E-mail address: maxim.puchkov@cincap.ch
[4]Right, First Time – Lab at RPD Tool AG
Infrapark Baselland, Rothausstrasse 61, CH-4132 Muttenz, Switzerland, www.rpdtool.com
E-Mail address: bernhard.schneider@rpdtool.com
*Corresponding author

***This contribution is an invited review paper, which will be published in Japanese in "PHARM TECH JAPAN". In the focus of this paper is the third dimension of FDA's Critical Path Initiative: "The Pharmaceutical Industrialization Process". The three authors suggest to adopt in the pharmaceutical industry the concepts and the workflow of the automotive industry (Pioneer: TOYOTA) to design, optimize, and test the vehicle first in silico. In the pharmaceutical industry it is possible to use an appropriate design and development software tool, such as CINCAP F-CAD (Formulation – Computer Aided Design) for designing and testing the drug delivery vehicle such as a tablet formulation for the first stage of clinical trials. For this purpose, pre-formulation studies have to be reengineered and a galenical drug-excipient screening program needs to be introduced (See topics of Pharmatrans Sanaq Forum 2013: www.pharmatrans-sanaq.com – Scientific Forum 2013). Prof. Dr. Hans Leuenberger had a chance to give, on January 14, 2013 a presentation on the topic of the Scientific Forum 2013 « Right, First Time » Concept and Workflow at the United States National Science Foundation ( NSF) in Arlington VA, USA. With the permission of the editor of "PHARM TECH JAPAN", SWISS PHARMA has received the exclusive right to publish the English version.***

*Keywords: Paradigm shift, galenical screening program, work flow of the aircraft and automotive industry, Quality by Design (QbD), formulation – computer aided design, percolation theory, in silico experiments, response surface methodology, tablet formulation design .*

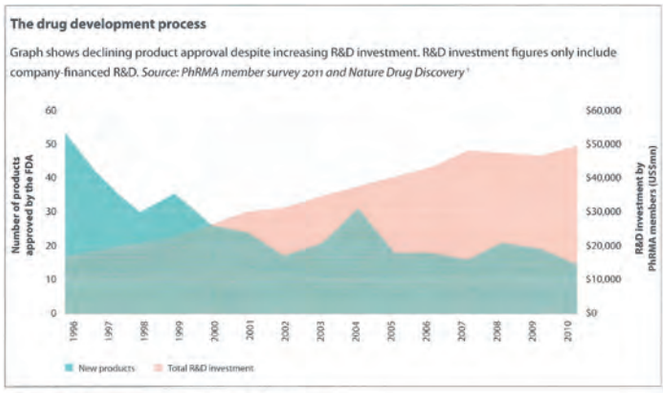
### 1 Summary

The continuously increasing costs of developing innovative drugs, the decline of the number of drugs registered per annum and the partly insufficient quality of the submissions prompted FDA to push forward several important initiatives such as the Critical Path Initiative, the Process Analytical Technology (PAT) Initiative and the Quality by Design (QbD) Initiative. FDA is especially concerned about the fact, that the products of the pharmaceutical industry have as a mean a standard of *two-sigma* quality, which is low compared to the chip manufacturing industry with a *six-sigma* quality. In this context the early workflow of the drug development has to be carefully analyzed, right at the stage of pre-formulation studies before doing the first clinical trials. It became evident, that an important paradigm shift needs to be introduced to be able to perform a lean *six-sigma* development. In this context the top management is challenged to abandon the classical workflow to use in the early phases of the development a simple service dosage form such as a capsule formulation to check the performance of a new drug substance. To achieve a *six-sigma* quality of the final marketed dosage form, it is important, that the first clinical trials are already done with a dosage form of *six-sigma* quality. It is a prerequisite, to do it "Right, First Time". Such a paradigm shift is however only possible, if the costs do not explode, as the classical workflow has been adopted due to the fact, that the attrition rate of NCEs in an early phase is still high and no company wants to waste money for nothing. For this reason, it is important, that the pharmaceutical industry adopts the workflow of the automotive and aircraft industry, i.e. to design and test the vehicle of transport first fully *in silico*. Such a paradigm shift is possible by using an appropriate software, such as F-CAD (Formulation – Computer Aided Design), which is allowing to set up and explore the formulation design space according to ICH Q8 (R2) and to take into an account the percolation theory. Thus, expensive laboratory work can be significantly reduced and only very few laboratory validation experiments need to be carried out in this early phase. This paradigm shift, using contemporary software, – should be complemented by the introduction of robotic technology to automate *preformulation* tests such as drug-excipient compatibility studies, accelerated stability tests of the final marketed dosage form, etc. For an optimal application of F-CAD it is important, that the drug and the excipients are well characterized according to their functional influence on the formulation properties. For the choice of the right excipients, it is recommended not only to per-

form a chemical drug-excipient compatibility study, but to perform also a galenical drug-excipient screening program using a mechanical simulator of a high-speed tabletting machine, such as Pressster™. The use of F-CAD and the use of selected preformulation studies, which do not need a lot of drug substance are important, as at such an early phase only a limited amount of drug substance is available.

## 2 Introduction: Industrialization as a critical path

The efforts by the pharmaceutical companies to put a new drug on the market become more and more expensive. At the same time, the number of successful registrations of a new drug per annum is decreasing according to FDA statistics (see Fig. 1 [1]). In addition FDA is concerned, that the quality of the pharmaceutical products is in the average only ca. *two-sigma,* i.e. far away from the quality of the champion, the semiconductor industry, with a *six-sigma* performance. This situation prompted several important initiatives of FDA such as the Critical Path Initiative [2], the Process Analytical Technology (PAT) Initiative, and the Quality by Design (QbD) Initiative – leading to the ICH Q8 document [3]. The corresponding author of this paper was involved in the PAT Initiative [4]. Since the implementation of these initiatives, the situation did not change significantly [5]. The three dimensions of the Critical Path Initiative (see Fig. 2) are still fully valid. Thus, there is a need for action. The authors of this paper put the focus on the third dimension: the industrialization process, especially the workflow in the early stage of drug development, i.e. the pre-formulation studies and the first clinical trials.




[1] Mullard, A, *Nature Reviews Drug Discovery* 10, 82-85 (February 2011)

Fig. 1: Rising costs of drug development and decreasing number of new registered products at FDA [1,5].

The Critical Path Initiative of FDA was a consequence of the still high attrition rate of drug products in the pipeline in the clinical phases I-IV. Most of the failures are due to problems, which occurred in one of the three dimensions of the critical path (see Fig. 2).

### 2.1 The service dosage form for Clinical Phase I

The analysis of the actual workflow at the early phases of drug development reveals a major flaw, that the first dosage form – (i.e. the so-called "service dosage form") to explore in the clinical phase I the efficacy of the drug substance and to search for the appropriate therapeutic dose – is usually a simple preparation, very often a capsule formulation, having as main ingredients a mixture of a filler (hydrophilic lactose) and of the drug substance, which is often of hydrophobic nature. In general the effects of percolation theory are not taken into account and catastrophic changes in the dissolution behavior of the formulation can occur [6–9]. It is important to realize, that the percolation theory affects any property of a formulation and is not limited to the drug dissolution rate or to a specific dosage form [10].The PhD thesis of Johannes von Orelli [11,12] had the focus on "Search for technological reasons to develop a capsule or tablet formulation" and shows clearly the advantage of a tablet formulation. The quality of a capsule service dosage form is often lower than *two-sigma* quality. Such a workflow has been adopted due to the fact, that the attrition rate of the number of drug substances in the pipeline is still rather high and no company is ready to spend a lot of money in an early phase of drug development for a drug substance, which may soon no longer be of interest due to – for example – toxicity or efficacy issues. This reasoning is valid taking into account, that extensive and expensive laboratory experiments to develop a robust formulation of *six-sigma* quality are needed. Due to the relatively high number of drug substances in the preclinical pipeline, the lack of human and laboratory resources and last but not least the lack of a sufficient amount of the drug substance available at that stage of development, a classical optimization of the simple service dosage form into a high quality, market-ready tablet dosage form of *six-sigma* quality for a Clinical Phase I study is not at all possible. Thus, the development of the market ready dosage form, often a tablet formulation occurs usually only after the drug substance has successfully completed clinical phase II (e.g. phase II c). According to the study of S. Schreder published in SWISS PHARMA [5], the attrition rate, which has been observed in Clinical Phase III is still high. This high rate has been related to lack of efficacy, lack of safety, commercial/financial and non-disclosed reasons. Interestingly, lack of efficacy, and lack of safety are clearly part of the Critical Path Initiative. Commercial/financial and no disclosed reasons may be also linked to the Critical Path Initiative, i.e. to the industrialization process. Problems in the industrialization process are many-fold and of different origin and cover the range from Clinical Phase I till Clinical Phase IV including the scale-up process, which consists of many hurdles if the formulation is not robust.

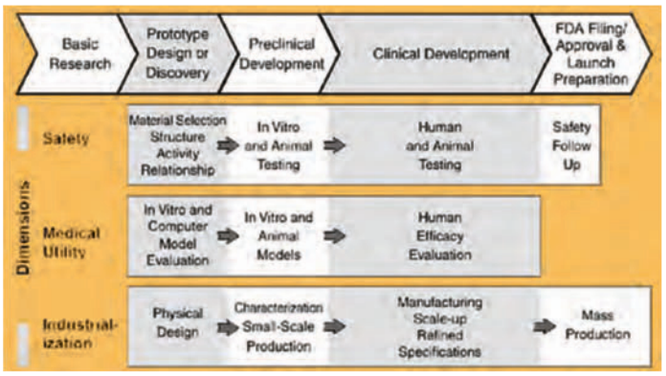



Fig. 2: Three dimensions of FDA's Critical Path Initiative [2]. The focus of this paper is the industrialization process.

### 2.2 Scale-up process: Enlargement of the batch size

An important part of the industrialization process is the scale-up of the batch size of the drug substance itself and of the drug delivery system such as a capsule or tablet formulation [13–21]. In general a tablet formulation is preferred being cheaper and in case of higher doses more convenient for an oral administration, than a capsule formulation. The pharmaceutical industry is aware of the critical path of the industrialization process: There are companies and Institutions trying to establish expert systems, to establish in-house data banks, in order to exploit the huge collection of in-house data of the batch to batch document system. A narrow and limited insight in such an attempt to exploit the data of tablet properties of batch documents was obtained with the PhD thesis of Lars Re-

horic [22] at the University of Basel. The batch concept has a lot of advantages, as a batch is a clearly defined quantity and can be accepted or rejected by the final quality control [23]. Unfortunately, the equipment for the scale-up of the batches is not designed according to the requirements of the scale-up theory [14–21]. It is important to identify scale-up invariants and to follow the physical laws of scale-up [14]. It is possible to simulate *in silico* the unit operations such as the wet agglomeration of particles in a fluidized bed granulation and drying equipment [18–20]. Thus, it is possible to establish transfer-functions for a computer-assisted scale-up of batch processes [19, 20]. To the knowledge of the authors of this paper no company has used so far such an opportunity of a computer-assisted [18] scale-up exercise. It is also a pity, that the curriculum of the studies of an industrial pharmacist does not contain the topic of scale-up.

Due to the intrinsic problems of the batch concept, major companies have started to spend a lot of money by looking for completely other avenues such as continuous processing, e.g. with the focus on the continuous granulation process hoping to achieve *six-sigma* quality of the final product. Unfortunately, a continuous process is much more complex than a one-pot batch unit operation. This is due to the fact, that a continuous process is only robust after reaching its dynamical equilibrium [17]. Thus, it is not easy to define in case of a continuous granulation process a batch size with a lot number, related to an amount of granules to be checked and released by the quality department for further processing. Such a wet agglomeration process is often a necessity to improve wettability and flowability of the intermediate granulated product to be compressed to tablets. In specific cases the wet agglomeration can be replaced by a continuous dry compaction. In such a case, it is important to take care of a possible work hardening of the material to be compressed and to verify, if wettability of the drug substance is a problem.

In the early phase of the drug development, it has to be kept in mind, that only a limited amount of drug substance is available, i.e. that the batch concept and the production of small batches have a clear advantage. In addition, as already mentioned, the quality of this clearly defined batch size can be accepted or rejected. For this reason a semi-continuous granulation process based on a small batch size (subunit) of ca. 6 kg is the process of choice [21]. Another advantage of the batch process consists in the possibility to measure the torque or the power consumption [15] and to be able to understand the resulting power or torque profile. In this context, special care has to be taken concerning the signal/noise ratio of the power or the torque signal. In addition, a deeper understanding of the wet agglomeration process is needed [14]. Unfortunately, most of the formulators do not really exploit the wealth of information, which contains the power consumption or torque profile [15]. In fact, the profile can be used for an in-process control in case of a semi-continuous process equipment [21], or can be used for scale-up purposes [14]. Most of the time, the profile has been just used as a fingerprint, only.

The semi-continuous granulation process line was successfully developed by Glatt AG [21] and had been tested at Roche [21] and at Pfizer [24] in the manufacturing department. It was possible to use the semi-continuous granulation line for placebo formulations and for formulations, already introduced in the market without changing the formulation [21]. According to Werani et al. [24], the semi-continuous process could be successfully applied also in the Pfizer manufacturing department at Freiburg, Germany. However, it is important to keep in mind, that such a granulation and drying line makes only sense as a part of the concept "Right, First Time". Thus, the first granule formulation, i.e. subunit of ca. 6 kg batch size should be designed, optimized and manufactured in the development department. Thus, a transfer from the same equipment in the development department to the same in the manufacturing department should not present any hurdle. An isolated solution as in the case of Pfizer and Roche is not an option and does not pay back. Thus, the equipment did not survive a reorganization of the management, despite the fact, that up to n = 100 subunits (= 600 kg) of granule formulations could be manufactured without an intermediate cleaning of the granulation and drying equipment [21]. In this context, it is important to realize, that the scale-up problem is no longer linked to the change of the physical dimensions from a small to a large manufacturing equipment, but is transferred into the fourth dimension, i.e. the time "t". Thus, the longer the equipment can be used without a necessary intermediate cleaning, the better is the scale-up problem resolved [25].

The holistic concept of "Right, First Time" is a must, as there is no equipment available, which is able to perform miracles, if the initially developed granule or tablet formulation contains major weak points. In other words, there exists no equipment, which transforms an existing *two-sigma* formulation into a *six-sigma* formulation, if the optimization work was not done, "Right, First Time".

### 2.3 Test for bioequivalence between the early service dosage form and the final marketed dosage form.

Another typical problem is the failure of the bioequivalence test of the service dosage form compared to the final marketed dosage form. Such a failure in Phase III may significantly slow down the time to market, if the formulation needs to be changed and some clinical studies need to be repeated.

In the classical workflow (see Fig. 4, Classical Workflow) it is a prerequisite, that the bioequivalence test between the initially used capsule formulation as a service dosage form and the final marketed tablet formulation is successful. For this purpose the newly developed final marketed tablet formulation should show the same in-vitro dissolution profile in the different media (pH 1.2; pH 4.5. and pH 6.8) as the service dosage form. Subsequently, it can be expected, that the final marketed dosage form complies with the bioavailability of the service dosage form.

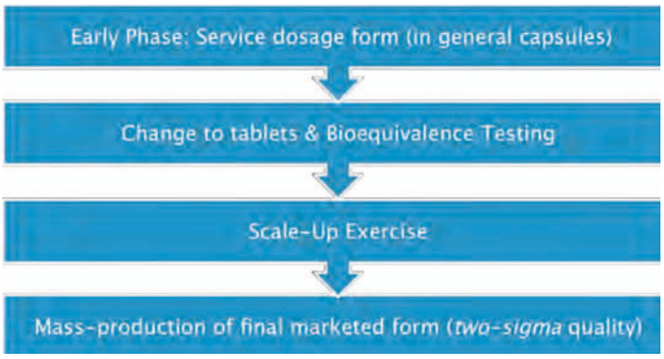



Fig. 4: Classical Workflow: The earlier service dosage form, i.e. in general a simple, not optimized capsule formulation is often replaced later by a tablet as the final marketed dosage form. It is generally recognized, that the quality of the final marketed dosage form is ca.*two-sigma*.

## 3 "Right, First Time" Concept and Workflow

It is difficult with the classical concept and workflow to improve the quality of the final marketed dosage form to the level of *six-sigma* quality. In this context, it has to be taken into account, that according to the safety regulations no major change in the formulation during the clinical studies is allowed to avoid the necessity to repeat expensive earlier clinical and toxicological studies. For this reason, the following paradigm shift becomes a must leading to the "Right, First Time" Concept and Workflow (see Fig. 5).

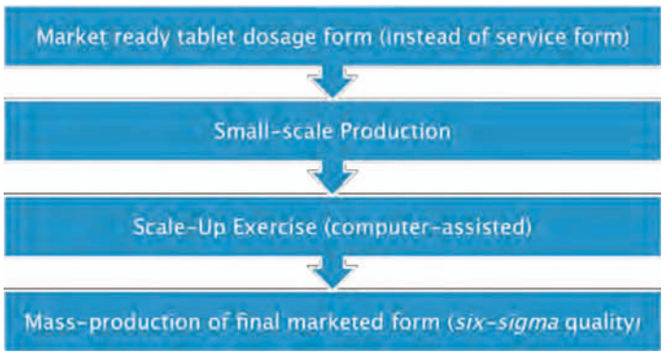



Fig. 5: "Right, First Time" Workflow: For the first clinical trials a robust *six-sigma* quality tablet prototype is used. All collected data since Clinical Phase I can be used for further optimization of the prototype. No bioequivalence test is needed. Stability data at R.T. of the prototype formulation being close to the final marketed dosage form can be used for registration purposes etc.

There are a number of prerequisites/requirements to obtain a *six-sigma* quality of the final marketed dosage form, as well as there are a number of critical processes, which need to be taken care of during the scale-up process, which are discussed in the following sections.

## 4 Requirements for the "Right, First Time" Workflow: Reengineering pre-formulation studies

Pre-formulation studies include an in-depth physico-chemical characterization of the drug substance and – if not provided by the excipient manufacturers – of the functional excipients used in the formulation of the dosage forms.
An excellent batch to batch quality of the material (drug, excipients) is a prerequisite, and should not be put into danger in order to save money by changing the excipient provider without being sure of the quality of the same excipient having maybe a slightly better prize.
A good knowledge in material science of the formulator is recommended to be able to judge the effect of changes in physico-chemical properties such as e.g. number of crystalline defects in a drug substance of a new crystallization process.
In addition to the physico-chemical characterization of the pure drug substance and the pure excipients, it is important to know chemical and physico-chemical as well as "galenical" interactions between the drug substance and the functional excipients used in the formulation. The choice of the type and quality of the primary material used should not be underestimated: Any manufacturer, who wants to sell a product of high quality, is aware of this fact. In this context, it is important to keep in mind the view of an architect, that the quality of the foundations determines the long term stability of a construction.

### 4.1 Physico-chemical characterization of the drug substance and of the functional excipients used in dosage form design

The following physico-chemical data of the drug substance (API) are needed: Solubility of API in different solvents and buffer media (at different pH values taking into account ionic strength), intrinsic dissolution data, particle size and shape distribution, true density, crystal shape, SEM micrograph, polymorphic modifications, salt type, possible pseudo polymorphs, loss on drying, residual content of solvents of the crystallization process etc. It is recommended to have a close contact to the in-house or external drug manufacturer to know the synthesis and the crystallization process [26].

An important issue is the selection of the salt of a drug substance used for the toxicology and clinical studies. The stability of the drug substance solubilized in different buffer media should be tested based on the law of Arrhenius. Thus, accelerated stability tests are a prerequisite for designing the first formulation of an injectable dosage form, which is a must to determine the pharmacokinetic data and the absolute bioavailability of the drug substance in animals and later in the clinical study. For the formulation of the sterile, liquid dosage form, additional excipients may be needed as well and tested for compatibility with the drug substance in solution.
In this context, it is important to check, if the properties of the excipients supplied comply with the certificate of analysis delivered by the manufacturer/provider. If needed, i.e. relevant, additional properties should be quantified such as true density, polymorphism, crystallinity, particle and shape distribution, pH value of a suspension of excipient particles in water, content of heavy metals, absence of microbiological contamination etc.

### 4.2 Chemical and physical drug-excipient compatibility study

In order to achieve an acceptable shelf life of the solid dosage form of 3–5 years at Room Temperature, a physico-chemical drug-excipient test to choose the compatible excipients is an absolute prerequisite. There are different types of tests predicting chemical drug-excipient interactions ranging from thermal analysis, functional group studies to accelerated stability tests at different storage conditions. It is not difficult to find in literature or by google suggestions, how to design a drug-excipient compatibility study. The corresponding author has published a factorial design for drug-excipient powder mixtures [27].

| Factor | Level | Conc.(excipient) | |
|---|---|---|---|
| **A** | –1 | Lactose | 69% (w/w) |
| (Filler) | +1 | Mannitol | 69% (w/w) |
| **B** | –1 | Stearic Acid | 5% (w/w) |
| (Lubricant) | +1 | Magnesium Stearate | 5% (w/w) |
| **C** | –1 | Maize Starch | 20% (w/w) |
| (Disintegrant) | +1 | MCC Sanaq burst | 20% (w/w) |
| **D** | –1 | PVP | 5% (w/w) |
| (Binder) | +1 | Hydroxypropylcellulose | 5% (w/w) |
| **E** | –1 | Dry (Dessicant added) | |
| (Storage Condition) | +1 | High Humidity | |

Fig. 6: Drug-excipient chemical compatibility program: Factorial design with 1% (w/w) API and functional excipients. The factorial design, based on the reference [27], has been slightly modified such as MCC is replaced by MCC Sanaq burst, a polymorph of MCC with superdisintegrant property [18] and the binder Gelatine is replaced by the pure synthetic product Hydroxypropylcellulose (HPC).

An accelerated stability test is the study of choice, which allows having a closer look to degradation products, which may be or not identical with metabolites, may need to be checked for pharmacological activity and/or toxicity etc. It is important to test the drug stability not just in binary drug-excipient mixtures, but in a more realistic environment of a mixture of functional excipients present in a solid dosage form [27]. Thus, it is possible to detect the effect of excipient-excipient-drug interactions, which can be helpful to achieve a prolonged shelf life of the dosage form.
Besides of the chemical drug stability, it is important to analyze as well the physical drug stability concerning polymorphic crystal

changes, formation of hydrates, eutectic interactions, hygroscopicity, crystal growth effects, etc. Today, it is possible to reduce expensive laboratory work by using standardized and automated test equipment, e.g. provided by RPD Tool AG [28]. Such an automated testing facility (see Fig. 7) contains storage cabinets to storage test samples under controlled conditions (humidity, temperature). In addition analytical tools are integrated to perform physical (i.e. Raman spectroscopy for morphological stability, near infrared (NIR) spectroscopy for hygroscopicity, camera for monitoring discoloration and other optical changes) and chemical (i.e. liquid chromatography) analysis. The data basis generated by such an automated system enables a comprehensive stability assessment of the formulation candidates.

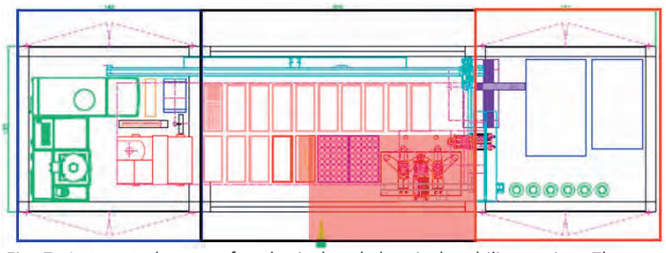


Fig. 7: Automated system for physical and chemical stability testing. The system consist of a set of racks (middle) for the storage of up to 1000 test samples under controlled conditions (temperatrue., humidity), several devices for non-destructive physical (camera, near infrared & Raman spectroscopy (left side)) and chemical (UPLC/MS, (right side)) analysis after automated sample preparation (red-colored area).

### 4.3 Automated accelerated stability test program for shelf life estimation of the final marketed solid dosage form

Pioneering methods for using stability data generated under accelerated storage conditions for shelf-life calculation under more realistic conditions were elaborated by K. Waterman et al. [29].
Although the published protocol and procedures yield in many cases accurate results, a significant number of studies remain where the simple approach with the extended Arrhenius function gives unsatisfactory or even false results. Some of these discrepancies can be explained, by e.g. a further decomposition of the initial breakdown products. In other cases however, the existing data generated according to the protocol given in [29] are not sufficient large enough for an in-depth analysis of the reason for the failure of the modified Arrhenius equation to predict the shelf life under realistic conditions.
For a more robust extrapolation of accelerated stability data to realistic conditions, it is therefore essential to use extended study designs which include more store conditions (temperature, humidity) and which provide larger analytical data sets. Last but not least it is also recommended to use latest analytical equipment such as UPLC including both UV and MS/MS detection in order to ensure a qualitative and quantitative correct interpretation of the degradation of the drug in the formulation during storage and to ensure a proper analysis of the corresponding kinetic profile. In numerous studies, the protocol given in table 1 has been worked out and is an appropriate approach to ensure a good data basis for a reliable shelf life estimation of formulation candidates based on accelerated stability data:
According to this extended protocol, up to 65 chromatographic analyses are performed within the scope of an accelerated stability study for each formulation candidate. It is therefore obviously that such a high work load requires fast analytical methods as well as automation in sample storage and chromatographic sample preparation. A Waters H-Class Acquity UPLC System with UV and MS/MS detection in addition to automated multi climate cabinets and chromatographic sample preparation systems are suitable equipment

| Conditon/Storage time [day] | 0 | 2 | 3 | 8 | 10 | 12 | 16 | 21 | 28 | 32 | 45 | 62 | 92 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 40°C/dry | | | | | | | | | | 1 | 1 | 1 | 1 |
| 40°C/60%RH | | | | | | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| 40°C/85%RH | | | | | | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| 45°C/dry | | | | | | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| 50°C/dry | | | | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | |
| 50°C/60%RH | | | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | | |
| 50°C/85%RH | | | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | | |
| 55°C/dry | | | 1 | 1 | 1 | 1 | 1 | 1 | | | | | |
| 60°C/dry | | 1 | 1 | 1 | 1 | 1 | | | | | | | |
| 65°C/dry | 1 | 1 | 1 | 1 | 1 | | | | | | | | |

Table 1: Extended study protocol for accelerated storage stability studies. Every number (1) represents a chemical analysis (UPLC/MS/MS) of a test sample.

to generate the analytical data in the required quality and with the required efficiency.
Data evaluation for shelf life estimations can be performed according to the procedure described by Carella [30] and starts with the calculation of the reaction rate constant (k) for the by-product formation at each storage condition by assuming a zero-order kinetic (c [t] = kt). The determined reaction rate constants k were then entered into the modified Arrhenius equation [29, 30] in order to calculate the shelf live at ambient conditions. It was found that in most cases reliable shelf life estimation can be performed after approximately one month storage, and after two months a final assessment of the chemical stability of the formulation is possible.

### 4.4 Galenical drug – excipient screening program

Different examples for a chemical drug-excipient compatibility program concerning the best choice of excipients for an optimal shelf life of the dosage form can be found in literature. Thanks to the education of the industrial pharmacist in chemistry, the interpretation of the drug-excipient compatibility program is no problem. Interestingly, in the case of the best choice of excipients to achieve an optimal, i.e. robust formulation, a corresponding literature search does not lead to any meaningful result. This fact may be linked to the traditional thinking, that formulation is considered more as an art than a science [4]. Due to the lack of a systematic galenical drug-excipient screening program, most of the formulations in the marketplace show the typical signature of the pharmacist, who has designed the formulation. In principle, a standard galenical drug-excipient screening program can be designed similarly to a chemical drug-excipient program (see Fig. 6) by preparing a tablet consisting of the drug substance mixed with a filler in different ratios combined with additional auxiliary substances such as a disintegrant and lubricant, using appropriate concentrations of the functional excipients. It is recommended to include e.g. up to three drug concentrations, covering possible geometric phase transitions, i.e. critical concentrations below and above the drug percolation threshold. The excipients chosen should be chemically compatible with the drug substance. The careful interpretation of the galenical screening program needs a firm knowledge in material science and powder technology, which is not part of the standard curriculum studying industrial pharmacy. A study in chemistry is not sufficient. It makes sense to have a standard galenical screening program for an immediate release and for a controlled release formulation and to check the relevant galenical tablet properties such as tablet disintegration time, drug dissolution profile, hardness and friability of the tablet. It is recommended to test the formulations as a function of time and storage in different climate conditions. Unfortunately, it is not known, if an accelerated stability study at higher temperatures may yield reasonable results concerning the prediction of the long term stability of physical tablet properties such as disintegration time, drug dissolution rate etc. There exist reports about "aging" of certain tablet formulations, which can lead to changes in relevant tablet properties such as the disintegration time. Thus,

an early detection of such a weak point in a formulation is an advantage. Often galenical properties such as hardness, disintegration time are determined as a function of the "applied" pressure. Such a description of the tableting process has become – unfortunately – part of the common language of an industrial pharmacist despite the fact, that the "pressure" is not an independent variable, but the result of squeezing material confined in a die between the upper and the lower punch surface.

Thus, especially in case of a standard galenical screening program, it is important to keep in mind, that the pressure developed is a material property. In addition, it is essential to study in detail the tableting process. For this purpose, it makes sense, to use an instrumented tableting device, capable of simulating mechanically a high speed rotary tableting machine such as the Presster™ (see Fig. 8 [13]). It is wise to use the Presster® as an analytical instrument in an early screening phase and not for finding a solution, how to repair a weak point of a formulation in a later phase. Fig. 9 shows a factorial design for a screeing program of an immediate release formulation looking for the best disintegrant in the presence of a different amounts of drug substance, testing two types of fillers (Lactose, Mannitol) and two types of lubricants (Magnesium stearate, Stearic Acid). The data, collected by the Presster™, using a constant gap between the punches, yield important results concerning the compaction process (see Fig. 10). The gap between the punches determines the thickness of the tablet, which is relevant for blister packaging. The mass of the tablet compressed in the die of the above specification determines the porosity of the tablet and the resulting pressure response of the material used in the formulation.

Fig. 8: Presster™ Compaction Simulator of MCC [13] simulating mechanically a high speed rotary press needing a small amount of material to be tested.

| Factor | Level | Conc.(excipient) | Drug Substance (API) |
|---|---|---|---|
| **A** | –1 | Lactose 71% / 10% API; | |
| | | 41% / 40% AP I; 11% / 70% API (w/w) | |
| (Filler + API) | +1 | Mannitol 71% / 10% API; | |
| | | 41% / 40% AP I; 11% / 70% API (w/w) | |
| **B** | –1 | Stearic Acid | 1% (w/w) |
| (Lubricant) | +1 | Magnesium Stearate | 1% (w/w) |
| **C** | –1 | Maize Starch | 15% (w/w) |
| (Disintegrant) | +1 | MCC Sanaq burst | 15% (w/w) |
| **D** | –1 | PVP | 3% (w/w) |
| (Binder) | +1 | HPC | 3% (w/w) |
| **E** | –1 | Low | 10800 tablets/h |
| Speed of Tabletting | +1 | High | 108000 tablets/h |

Fig. 9: Example of a factorial design for a galenical drug-excipient screening program for the best technological choice of the functional excipients.

| Result | D1.2 | D1.3 | D1.4 | D2.2 | D2.3 | D2.4 |
|---|---|---|---|---|---|---|
| **UC Peak (kN)** | 58.9 | 37.1 | 13.1 | 39.7 | 19.1 | 5.5 |
| **LC Peak (kN)** | **55.5** | 37 | 14.1 | 39 | 19.8 | 6.2 |
| **Peak Eject (N)** | 134.2 | 78.8 | 121 | **2095.7** | **1306.3** | 493.8 |
| **Take-Off (N)** | **2.1** | 1.6 | 1.3 | 1.1 | 0.9 | 0.8 |
| **Weight (mg)** | 504.9 | 506.2 | 506.4 | 504.7 | 505.2 | 504.3 |
| **Thickness (mm)** | 4.52 | 4.58 | 4.8 | 3.64 | 3.82 | 4.27 |
| **Hardness (N)** | >300 | **>300** | **>300** | **144** | 91 | **19** |
| **Disint. time (sec)** | 454 | 426 | 174 | 35 | 12 | 6 |

Fig. 10 Results of the Presster™ [33] including tablet properties (Thickness, hardness, disintegration time measured 24 h after production): The differences in the results as a function of the excipients used are impressive. A high ejection force is related to a **problem concerning lubrication.** A high take-off force can lead to **sticking problems.** A high response of the pressure at the constant gap distance can have as a consequence a higher weir of the tableting tools (punch abrasion).

## 4.5 Tableting problems, which can occur during scale – up, resp. the industrialization process

The following tableting problems can occur specifically during scale–up exercise, using high performance tableting press equipment with high tableting speeds:

1) Lubrication problems
2) Sticking of the tablets
3) Capping of the tablets

As the Presster™ results show, there are clear differences visible concerning the ejection force, which can be related to a possible lubrication problem. A high take-off force can be related to a sticking problem. The problem of capping is a critical one, as it occurs only at higher tableting speeds, and sometimes only after a certain time. Thus, it is important to perform the tests with the Presster™ Compaction Simulator during the pre-formulation studies. Further studies need to confirm, if a high percentage of elastic energy during the compaction work is a save indicator for a possible hidden capping problem. On the other hand, a test of the ratio between the indentation hardness of a tablet and its tensile strength can serve as an indicator of a capping tendency (see Fig. 11 [34]).

It is important that the Presster™ equipment can simulate mechanically a rotary high speed press using only a limited amount of material to be compressed. The effect of the tableting speed on the properties of the tablets [33] is shown in the Fig. 12.

To be on the safe side, it is important to perform these experiments with the Presster™ equipment, using an appropriate experimen-

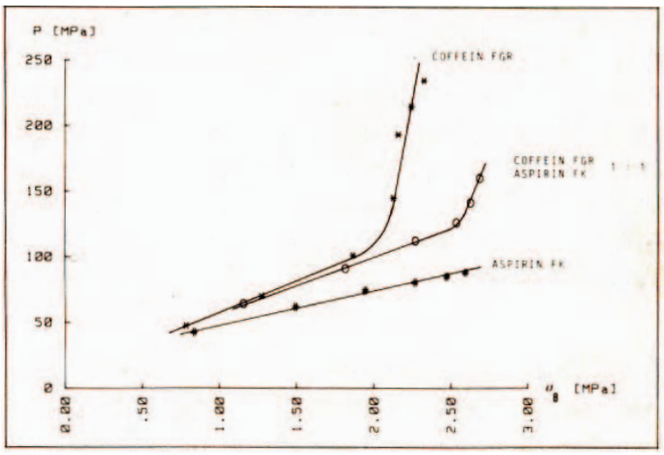



Fig. 11: "Capping Propensity": Indentation hardness/tensile strength ratio values of tablets not yet showing the problem of "capping" as a function of the peak value of the compression force in order to obtain harder tablets of Caffeine FGR, Acetylsalicylic Acid (Aspirine FK) and a mixture 1:1 [34]. The ratio, i.e. the slope of the line is constant, if no capping occurs. The tendency of capping becomes visible due to a change in the slope, as the tensile strength is sensitive to small cracks within the tablet before real capping occurs. In this context the indentation hardness is a « local » property of the tablet, but the « tensile strength » depends on the global structure of the tablet. The direct compressible Aspirine FK did not show any capping [34].

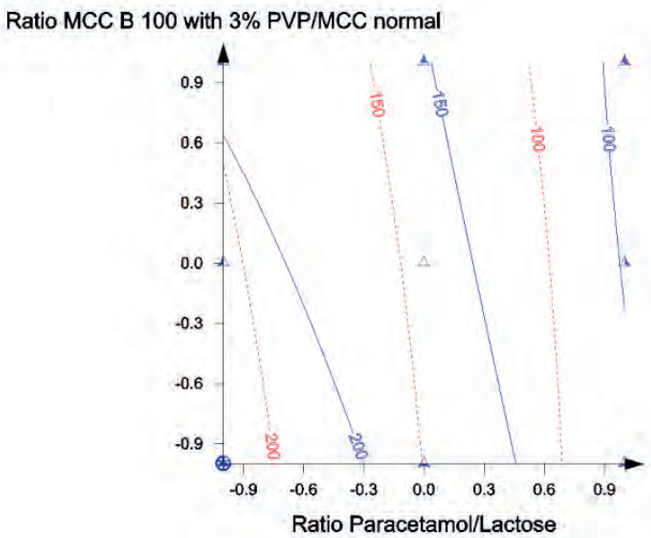



Fig. 12: Formulation Design Space Exploration according to ICH Q8 R2: Effect of the tableting speed on the hardness [N] of Paracetamol tablets [33]. It has to be kept in mind, that due to the application of a response surface methodology according to ICH Q8 (R2) using a quadratic order approximation, the response surfaces show always, either, a maximum, a minimum or a saddle point. Thus, a "canyon" as a result of a possible percolation threshold [32] cannot be detected with such an approach. However, it seems to be evident, that the tableting speed, respectively the dwell time during the compaction process has an effect on the hardness value: The tablet hardness is lower with a shorter dwell time (i.e. high speed = red lines in [N]). Tablets have been prepared with the Presster™ compaction simulator [13] as a function of coded variables with a low ( = blue) and a high ( = red) tableting speed, yielding different results.

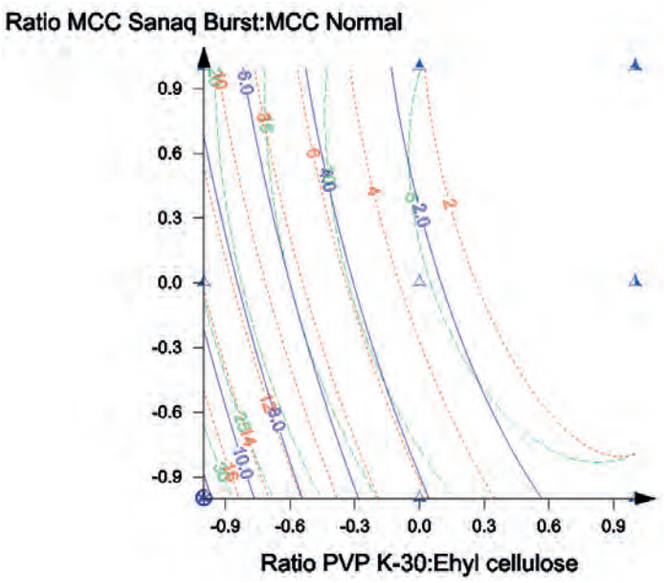



Fig. 13: Design space exploration of Nifedipine extended release matrix tablet formulations [33] according to ICH Q 8 R2: Results of in-vitro dissolution profiles of the time points t40% (blue), t60% (red) and t90% (green). Contour plots represent time lines [h] of 40%, 60% and 90% drug released in simulated gastric fluid [33].

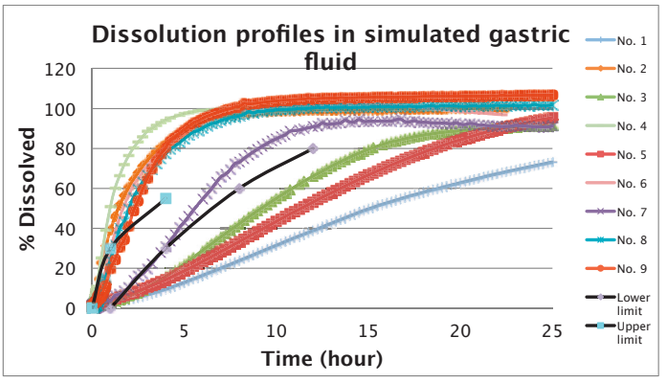



Fig. 14: In-vitro dissolution profiles of 9 Nifedipine 80 mg Extended Release Matrix Tablet formulations using the Presster™ Compaction unit in the framework of a drug-excipient galenical screening program according to ICH Q8 R2 [33] with Ethocel as Matrix, Microcrystalline Cellulose (MCC), Microcrystalline Cellulose Sanaq Burst a second generation product of MCC Sanaq Rapid [18] and PVP as solubilizing agent for Nifedipine. In the plot the USP dissolution specifications for the lower and upper limit for a 60 mg Nifedipine Extended Release formulation are included.

tal design according to the guidance of ICH Q8 (R2), see Fig. 13 and Fig. 14. However, it has to be kept in mind, that using only a factorial design for such an evaluation does not take into account percolation effects, i.e. it is important to know, if there are percolation thresholds, which may influence dramatically tablet properties [6,32]. For this reason, it is important to use F-CAD (Formulation – Computer-Aided Design), a software, which is able to detect percolation thresholds and in addition saves laboratory work.

### 4.6 Computer-Assisted Scale-up

Most of the actual unit operations are batch processes such as mixing, granulation, i.e. the wet agglomeration process [31] and the subsequent drying. Unfortunately, there are different types of mixers, granulators and dryers, which are different in size and differ in specific properties such as heat capacity, confinement properties, cleaning properties, hidden spaces, etc. It is evident, that the requirements for scale-up to fulfill the criteria [14,20] concerning geometric, kinematic and dynamic similarities are not given in prac-

tice at all. On the other hand, thanks to the requirements of FDA to keep batch records, there are plenty of data concerning the standard operation procedures and properties in case of small, medium sized and very large batches. Often these data [22] are not really exploited and represent a kind of cemetery of data, which can be checked for inspection, if needed. Indeed, such a wealth of important information could be easily used to define a "transfer function" for obtaining the same properties of an intermediate product for a small and a large scale batch. Thus, it is possible to establish a "computer assisted scale-up" exercise. Such an approach includes the creation of a specific Virtual Equipment Simulator (VES), which can be used also for training purposes [18, 19]. Flight Simulators are used since many years for the training of pilots. Fig. 15 shows the vision of the CINCAP VES system. It is evident, that such a VES needs to have a scientific backbone to calculate the transfer function, which will make the link between the small and large scale equipment (see Fig. 16). In case of continuous processes such as tableting (see Chapter 4.5) or the wet agglomeration process (granulation), other criteria such as the dynamical equilibrium [17] or time dependent scale-up problems having an identical geometry in case of a semi-continuous process [25] need to be taken into account. It is important to realize, that Virtual Equipment Simulators (VES) are also an excellent tool for equipment manufacturers to improve their equipment [18].

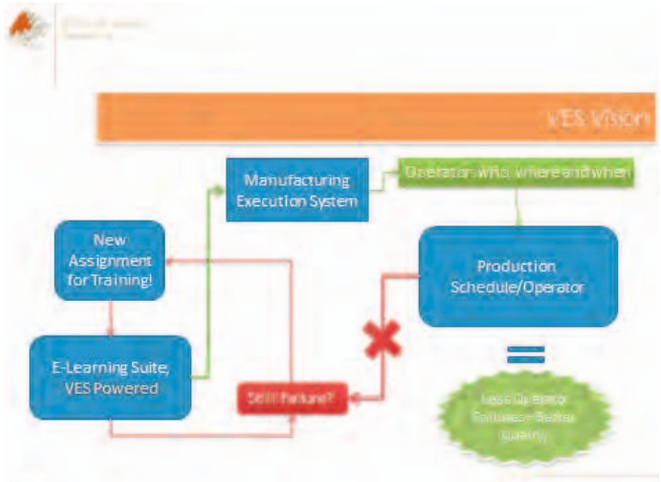



Fig. 15: Schematic representation of a Virtual Equipment Simulator (VES) used for a computer assisted scale-up and for training purposes (Courtesy: CINCAP LLC, Switzerland)

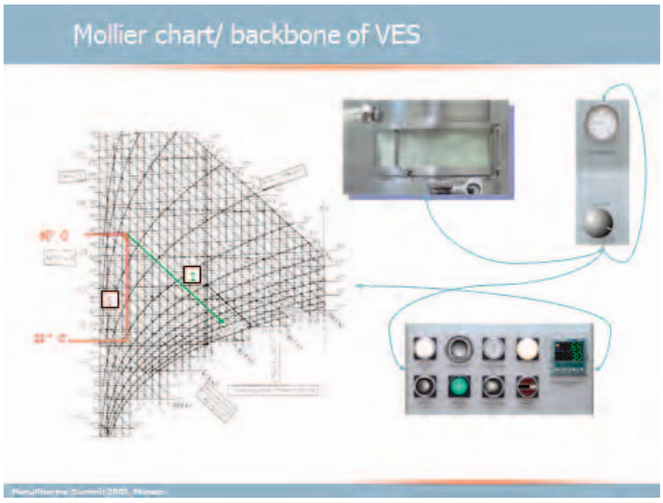



Fig. 16: Mollier chart as backbone of the Virtual Equipment Simulator of a Fluid bed Granulator and Dryer (Courtesy: CINCAP LLC, Switzerland).

## 5 F – CAD as a prerequisite for rapid prototyping of the tablet formulation ready for marketing

The goal is to test the drug substance already in Clinical Phase I with a prototype tablet formulation, which is optimized having *six-sigma* quality and does not vary significantly from the final marketed dosage form. A dosage form is a drug delivery system and can be compared to a transport vehicle, which transports drug molecules (like aircraft does with passengers) to the site of action. There is however a major difference between the automotive, respectively aircraft industry and the pharmaceutical industry: Today, the first prototype of a new car or an aircraft can be designed and tested fully *in silico*. Thus, there is a need to develop adequate software capable of designing a solid dosage form, such as a tablet. The software needs to be also capable of taking into account the effects of percolation theory, i.e. to detect percolation thresholds in the compressed powder bed of the ingredients (drug substance, functional excipients) being involved in the formulation. The software F-CAD (Formulation–Computer Aided Design) developed by CINCAP GmbH showed to be capable of calculating the dissolution profile of a drug substance [18] and to estimate the disintegration time of a tablet formulation [19,32,48]. F-CAD can be used to design an immediate and or a controlled drug release tablet formulation [35] and to detect percolation thresholds.
The availability of F-CAD allows to adopt the same workflow (see Fig. 5: "Right, First Time"-Workflow) as in the automotive, respectively aircraft industry. Thus, it is possible to fulfill the requirements of ICH Q 8 (R2) by exploring the formulation design space in an early phase of the drug development. It is even possible to design a tablet prototype with a *six-sigma* quality for the first clinical trials in Clinical Phase I. Thus, much more relevant data for a final optimization within the design space can be acquired during the subsequent clinical phases. No major change of the formulation or a bioequivalent test between an early service dosage form and the final marketed dosage form is required.

### 5.1 Selection of the best suited material for the *in silico* design of the drug delivery vehicle

The functional excipients used for the design of the drug delivery system, i.e. the solid dosage form needs to be chosen carefully. It is evident and generally recognized, that the functional excipients need to be chemically compatible with the drug substance. Interestingly, a systematic galenical screening program to select the best suited functional excipients is not yet a standard approach. The authors of this paper suggest selecting the best suited material for the *in silico* design of the drug delivery vehicle on the basis of the **chemical** drug-excipient compatibility **and** the drug-excipient **galenical** screening program.

### 5.2 Dose range finding and selection of the appropriate dissolution profile for the *in silico* design of the drug delivery system

Depending on the drug substance, its indication, its pharmaco-dynamic and pharmaco-kinetic profile, an immediate and/or controlled release drug delivery system needs to be designed. F-CAD (Formulation–Computer Aided Design) is capable of designing both types without problems. In this context, it is important to realize, that the calculation of the *in silico* dissolution rate is based on a first principle approach using cellular automata and is different from any known "expert system" being based on a collection of acquired "in-house" data, knowledge and expertise. The major difference of the F-CAD approach to an expert system is that F-CAD uses a calculation principle. This means that with the help of cellular automata-based algorithms the physical experiment (e.g. compaction of a power mixture

or dissolution testing) could be carried out in a computer memory, i.e. virtually. In this respect, the CAD-based approach is an attempt to "move" the real laboratory into virtual reality; and to carry out trials without spending precious substances and time. Such an approach does not involve stored human expertise but requires real expert to drive the development process. Generally speaking, there is no change to the standard approach in formulation R&D but the test could be made in "virtual laboratory", planned by a human expert.
Due to the fact, that side-effects of a medication often depend on the rise of the plasma level of the drug substance in the individual patient, it can be an advantage to design from the very beginning of the first clinical studies an immediate release and a slow release tablet formulation.
For clinical phase I it is important to design from the beginning a tablet with a small, a middle and a high content of the drug substance, which covers the range below and above the percolation threshold of the drug substance. The mass of the tablet should be chosen, which shall allow in steps a larger size of the tablet formulation to accommodate, if needed, a higher amount of drug substance for dose range finding.
As only a few laboratory experiments are needed for validation purposes of the F-CAD proposed formulations, there is no problem to spend too much money in this early development phase. Needless to say, how much in-depth and valuable knowledge during the subsequent non-critical path of the industrialization phase can be obtained with such a dosage form, which is already optimized and ready for marketing.

### 5.3 Tablet shape (Tablet Designer)

F-CAD has as a module to design first the shape and volume of the desired tablet (see Fig. 17). In an early, exploratory phase a simple geometry of the tablet is appropriate. However, if for marketing reasons, a more attractive or specific shape is desired, it makes sense to check *in silico* the influence of changing the shape of the tablet on the dissolution rate [18, 19, 35]. This step is an important task for the subsequent *in silico* unit operations to create the virtual *in silico* tablet [32, 35]. In this context, the true densities of the drug substance and the excipients are needed. It is important to check *in silico* the influence of the porosity on the drug dissolution profile and to make a decision on the porosity of the tablet.

### 5.4 F-CAD calculations

For the creation of an *in silico* tablet, corresponding unit operations as in case of laboratory experiments are needed such as direct compression, size enlargement of the powder particles (granulation process), addition of the outer phase with a disintegrant, lubricant.

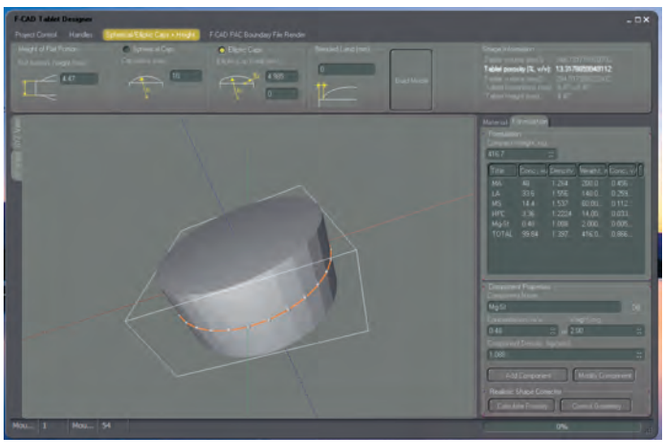


Fig. 17: Tablet designer (Screenshot) [32].

The details are part of the F-CAD training module and the application of these *in silico* unit operations are generally described in [35]. Thus, as an example, the "*in silico*" compression is based on a kind of "time-inversion"-process by letting grow the involved particles in the confined space of the die and the neighboring particles leading to a deformation of the shape of the original particles [32].
The major merit of F-CAD is its capability to calculate ab *initio* the dissolution profile [18, 19, 35] of a tablet formulation, an immediate and/or a controlled release one. A typical example is shown in Fig. 18.
For drug substances with a very low water solubility the tablet disintegration time is used as an important property of quality. F-CAD is not able to calculate the disintegration time, which depends on the equipment used (with or without disks). However, it can be assumed, that the "time elapsed" ($t_e$) till the water molecules reach the center of the volume of the tablet is to a certain extent correlated with the disintegration time (see Fig. 19). Further studies need to be done to check, how the situation could be optimized. Most important is, however, the capacity of F-CAD to detect percolation thresholds (see Fig. 19). This ability is of special interest in connection with ICH Q8 (R2) to explore in the early phase of the drug development the design space of the drug formulation.

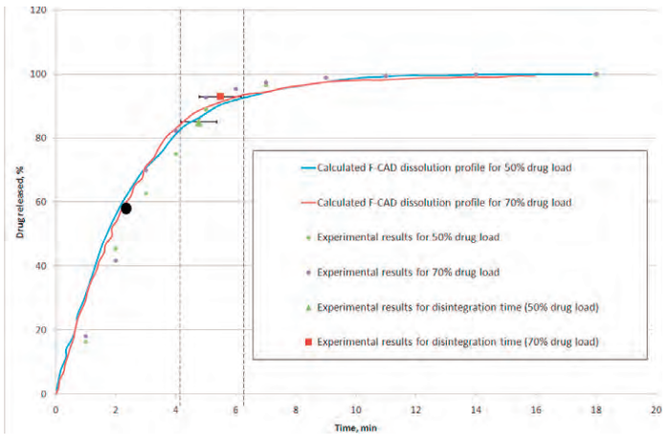



Fig. 18: F-CAD calculated drug dissolution profile with time elapsed ● till the water molecules have reached the center of the tablet and experimental values of the disintegration time [18, 36].

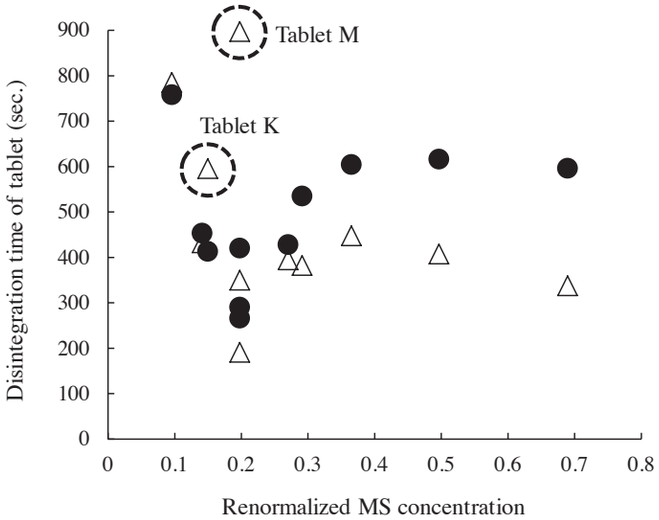



Fig. 19: F-CAD calculated values of the time △ elapsed and disintegration time in the neighbourhood of the percolation threshold [32].

## 6 The 3 "M" Dimensions of Excellence to do better and save money

In this context, the Swiss Watch Industry under the leadership of Nicolas Hayek of the Swiss Group SWATCH is an excellent showcase with an outstanding performance contributing a major part to the GDP of Switzerland thanks to the Excellence in the 3 "M" dimensions, i.e. Outstanding Excellence in lean and smart **M**anagement, in **M**anufacturing by an extensive use of robotics and last but not least an Outstanding Excellence in **M**arketing!

Indeed, a Lean *six-sigma* Drug Development is not sufficient, it must be also smart. It is important that the management puts the right priorities to achieve in a smart way the desired *six-sigma* quality. To save money at the same time, it is a prerequisite to replace as much as possible of expensive laboratory work. In this respect an outstanding Excellence in 3M (Management, Manufacturing, and Marketing) is most important:

Point Nr. 1, Excellence in Management: Introduction of the "Right, First Time" concept and workflow by replacing laboratory experiments by *in silico* design and testing being best practice and state of the art in the automotive and aircraft industry. As the introduction of the described "Right, First Time" concepts consists in a major paradigm shift affecting many working stations of the existing workflow, i.e. within the R&D and the manufacturing departments, some reorganization steps optimizing connectivity and smart management decisions are of primary importance for a holistic implementation. The potential savings are remarkable.

The aircraft industry [40] reported the following savings, which can be summarized as follows: Elimination of >3000 assembly interfaces, without any physical prototyping, 90% reduction in engineering change requests (6000 to 600), 50% reduction in cycle time for engineering change request, 90% reduction in material rework, 50% improvement in assembly tolerances for fuselage.

Indeed, it is estimated that at least comparable or even more savings can be expected in the pharmaceutical industry, especially, if F-CAD is used in a holistic approach within the context of the "Right, First Time" concept and workflow and not as an isolated solution [18, 19, 41]. Most important is the application of F-CAD to explore *in silico* the Formulation Design Space according to ICH Q8, as an "unlimited" number of formulations can be tested *in silico* for the appropriate drug release profile (see Fig. 20 [43]).

In Fig. 20, the *in silico* formulation design space exploration was performed as part of the classical workflow for the transition from the capsule formulation as a service dosage form to the final tablet formulation for the market. It is important to keep in mind, that the potential of F-CAD cannot be fully exploited in such an exercise, as a major change of the formulation is not allowed due to regulatory issues. Such type of "insular" solutions have been in the past a type of "repair actions" to correct weak points of an existing tablet formulation, which did not comply with the dissolution profile of the service dosage form or did not pass the bioequivalence test. Thus, no significant savings can be achieved due to the lack of a holistic implementation of the "Right, First Time" concept and workflow.

Point Nr. 2 Excellence in Manufacturing: It is important, that substantial savings can be achieved by using dedicated robotic equipment instead of investing in expensive manual labor. In this context, the Swiss Watch Industry is an excellent example replacing as much as possible manual work to manufacture first class watches at a reasonable prize.

In case of countries with expensive manual labor work, the use of robots to reduce costs is essential. FDA's Quality by Design (QbD) and PAT initiative boosted in-line, on-line and at line in-process controls [23, 42] and to a certain extent the use of robotics, however, the R&D departments still have room for improvements to use robotics, especially the area of *pre-formulation* studies such as determination of the physico-chemical properties of the drug substance, drug-excipient compatibility studies, accelerated stability tests for solid dosage forms [44] etc. AstraZeneca achieved substantial savings in the area of accelerated stability tests [45], using automated equipment of RPD Tool AG (see Fig. 21 a/b).

Point Nr. 3 Excellence in Marketing: Last, but not least, it is important to realize, that the concept and workflow of "Right, First Time" will reduce the time to market due to the fact, that a robust and market ready tablet formulation is available already at the time of the initial clinical phase and just needs to be refined in order to show optimally the therapeutic advantages of the new drug substance. Thus, such an approach will lead to better medicinal products which can be better marketed. This advantage of the "Right, First Time" concept and workflow is of special importance in case of a blockbuster product: The reduction of time to market will lead to savings of equal or more than one million USD per day being earlier on the market.

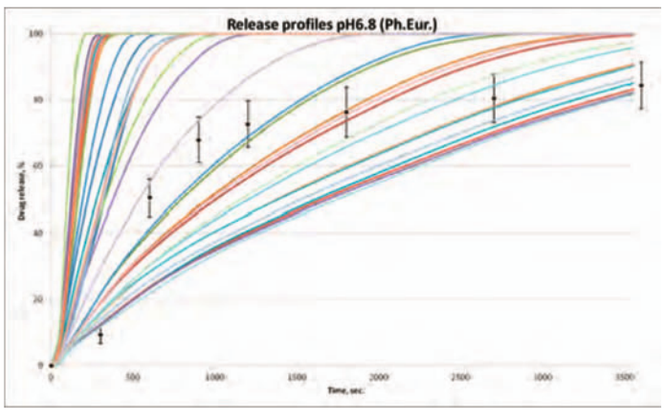
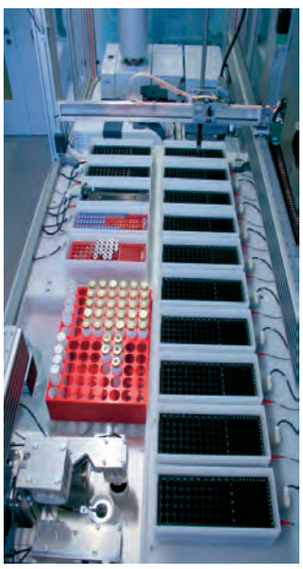



Fig. 20: F-CAD *in silico* Formulation Design Space Exploration according to ICH Q8 R2 testing the dissolution profile of 35 tablet formulations in phosphate buffer pH 6.8. The points with the error bar represent the in-vitro dissolution profile of the capsule formulation of the service dosage form [43] as reference for the final tablet formulation for the bioequivalence test (Classical Workflow with a capsule service dosage form of low quality as reference).



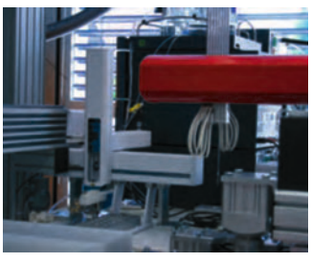


Fig. 21a

Fig. 21b

Fig. 21: a/b: Views of parts of the second generation robotized automatic stability test equipment having a size of 6 m x 2.5 m developed by RPD TOOL AG,(courtesy RPD TOOL, Switzerland).

## 7 Conclusions and Outlook

### 7.1 The Implementation of the "Right, First Time" Workflow

The first step consists in establishing a working party, preferably with an internal or external expert, for analyzing and comparing the existing workflow with the "Right, First Time" workflow. As the situation may differ from company to company different scenarios are feasible, which have to be taken care of.
The different scenarios need a different amount of investments to implement the holistic concept of the "Right, First Time" workflow:
A) Substitution of the service dosage form with the F-CAD optimized tablet formulation, which needs a minimum of investments and is a prerequisite.
Scenario A is recommended, if the company has no problems with scale-up exercises and if the degree of laboratory work being automated in the R&D department is already high. Ideally, the manufacturing processes are in case A also automated. Scenario A leads to the following idea to be checked with e.g. a case study in order to quantify the benefits, as at practically no cost a fast and a slow release tablet formulation can be prepared for Clinical Phase I. The two formulations with e.g. three different drug loads can be used for a more differentiated study than just a simple dose range evaluation. The additional investment in this early clinical phase needs to be, however, quantified taking into account, that the test dosage form has already *six-sigma* Quality, i.e. the variability of the clinical data cannot be attributed to a low quality service dosage form. On the other hand, it has to be kept in mind, that the number of drug substances at the end of the preclinical phase is still higher, than at the end of clinical phase I, creating additional costs for drug substances, which fail for other reasons. If no additional studies during Clinical Phase I are planned, the additional costs are modest and refer to the costs of the license of the software incl. training activities and to a galenical drug-excipient screening program in addition to the chemical drug-excipient program. The Return on Investment should be very high, to be sure to have already an optimal dosage form ready for the market at the early stage of Clinical Phase I.
B) The scenario B differs from scenario A by investments for an increased use of robotics in the area of R&D, using automated physico-chemical screening programs. Payback times of 1–2 years for the hardware needed to automate pharmaceutical-analytical screening tests have been reported.
C) Scenario C differs from Scenario A by investments in a computer-assisted scale-up process. In this scenario C, no change in the existing hardware of the manufacturing department is needed. The data of the batch records are better exploited and an investment is needed for the Virtual Equipment Simulators (VES). The use of VES will facilitate the continuous education and personnel training of the persons involved.
D) Scenario D differs from Scenario A by introducing in the R&D and in the Manufacturing Department identical hardware for manufacturing small scale and large scale batches, e.g. using a quasi-continuous granulation and drying line. This unique investment will avoid future scale-up problems and lead to short time pay back.
Last but not least, it is important to realize, that F-CAD is the backbone of the "Right, First Time" concept and workflow allowing all the responsible persons of the departments of the pharmaceutical industry involved, i.e. from R&D, Manufacturing till Registration, to check carefully the technical results before submitting the documents to the regulatory authorities. Thanks to the *six-sigma* quality of the dosage form in all clinical phases the lower variability of the drug delivery system will lead to important savings and shorten time to market. On the other hand, F-CAD is the tool of choice for FDA, EMEA, Swissmedic, i.e. for the regulatory authorities, for checking the internal consistency of the technical data in the documents, which have been submitted, helping to speed-up the acceptance process.

### 7.2 General Statements and Outlook

A paradigm shift in the actual workflow is a prerequisite to have a chance achieving a turnaround in the trend of Fig. 1 showing the constant rising costs of introducing a new drug into the market. The most important action to be taken will be the introduction of the workflow known as best practice in the automotive and aircraft industry, i.e. that the first prototype of the transport vehicle is first designed and tested completely *in silico*. Thus, the critical path of "industrialization" could lose its cliffs, which are costly and endanger a high quality of the formulation. Thanks to the better knowledge and thanks to a computer assisted scale-up exercise a *six-sigma* quality should be possible to be reached. According to the requests for writing book chapters on the topic of F-CAD and computer assisted scale-up [20, 46] the awareness of the pharmaceutical industry seems to increase. In addition, it is important to realize, that F-CAD allows the pharmaceutical industry and the regulatory authorities such as FDA, EMEA, Swissmedic, to validate and check the data submitted of consistency.
It is concluded that F-CAD software is one of the tools for the substitution of laboratory experiments for the purpose of the design and development of new pharmaceutical solid dosage forms with taking account for the exploration of the formulation design space according to ICH Q 8 (R2). Due to the steadily rising costs for developing and finally for registering a new drug substance, the pharmaceutical industry starts to use for a rapid pharmaceutical development more and more software tools. Such an approach is not new and has been successfully introduced in the automotive industry, with Toyota as a pioneer using the principle of "Quality by Design" [47]. Today, not only cars but also aircrafts such as the Boeing 777 and the Airbus 380 are first constructed and tested *in-silico.* Such an approach is considered as best practice. TOYOTA as a pioneer in this field showed, that it seems to be easier to achieve a top ranking, than to keep such a ranking.
In the study [32] the software F-CAD (Formulation-Computer Aided Design) [32] is used to calculate *in silico* the expected time of disintegration. F-CAD has been very successfully applied so far to predict the dissolution profile of a tablet [18, 19, 35, 36] and there is a conjecture, that the "time elapsed" till water molecules reach the center of the tablet, which can be calculated by F-CAD could be a surrogate for the effectively measured disintegration time.
From the point of view to choose the best experimental design to find critical concentrations, it is highly recommended to take into account the percolation theory. Thus, among others, the experimental range can be narrowed. The Dissolution Simulation (DS) module of F-CAD, which is based on cellular automata algorithm has been used to simulate the disintegration time of a Mefenamic Acid tablet. The experimental disintegration time of tablet is compared with the calculated specific time point for water to reach the geometric center of the tablet. In general, there is not a specific problem to calculate these specific times. The disintegration is the key property, especially for low water soluble drugs. Often the disintegration test can reduce the number of dissolution runs for the design and process development of immediate release tablet formulation at the early stage such as phase I and II before proof of concept study [32].
Thus, a "dangerous canyon" close to the percolation threshold leading to a high variability of a sensitive tablet property may not be detected by only response surface methodologies [32]. It is evident that such a design space exploration with classical laboratory experiments is extremely difficult to realize and would be extremely expensive. In this respect, the application of F-CAD opens a new research avenue, i.e. a "New Kind of Science" [37] in the language of Stephen Wolfram (Princeton University). Stephan Wolfram describes in his book a "New Kind of Science" [37] among others the use of Cellular Automata (CA) instead of solving partial differential equations such as the equation of diffusion of water molecules, which are responsible for the release of the drug substance, of

swelling of starch etc. In this context, it is important to know the corresponding "CA-rule", which copies the natural diffusion process in three dimensions. Classical science uses the classical tools of mathematics, algebra, higher analysis, complex calculus, differential and integral equations with the necessary boundary conditions in order to describe phenomena occurring e.g. in nature. Depending on the complexity of a problem, the use of these classical mathematical tools may represent a very challenging task and may need a lot of computer power to solve the problem numerically. Interestingly, the use of CA offers an *ab initio,* i.e. a "first principle" approach, which takes into account "automatically" the "boundary conditions" of the tablet shape, tablet volume, porosity, drug particle size, distribution of the different types of particles (drug substance, functional excipients) etc.

The results of this study show that the application of percolation theory is a must in order to detect percolation thresholds. It is important to know the response surfaces close to the percolation threshold of sensitive tablet properties such as the disintegration time to get information about the robustness of the selected formulation. In this context one has to put the question forward if the application of the percolation theory and the use of F-CAD to detect the percolation thresholds should be an integral part of the guidelines of ICH Q8 exploring the formulation design space [48].

There are clear indications, that the industrialization process can be improved and critical hurdles can be overcome. However, in this context, it is important to take several actions, i.e. 1) FDA, EMEA, Swissmedic, i.e. the regulatory authorities should take the lead for a clear guidance in this area and to develop solutions together with the industry. 2) The educational curriculum for an industrial pharmacist at the University level needs to be changed that the industrial pharmacist will be ready for the challenges of the industrialization process of a drug delivery system. Thus, the curriculum should consist of an excellent knowledge in biology, chemistry, mathematics and physics being the foundations of doing a major in industrial pharmacy. In addition special knowledge in higher mathematical analysis, material science, chemical engineering, pharmaceutical engineering, mechanical engineering, equipment engineering, scale-up theory and application, computational science for modeling and simulations, percolation theory should be part of the curriculum. A stage in industry of at least 6 months -1 year for a master thesis is a must. The curriculum and the degree should be validated, respectively certified by an appropriate body of FDA, EMEA, Swissmedic etc. The corresponding author of this paper had originally in mind as acting Head of the Institute of Pharmaceutical Technology, to start an initiative for an International PhD Program in Pharmaceutical Technology with the support of the pharmaceutical industry. The idea was boosted by a survey showing that more than 95% of all former PhD students of the corresponding author are working in the pharmaceutical industry. The idea was later abandoned, as some top managers of the pharmaceutical industry complained, that young people from University are in a very short time completely absorbed by the existing company culture, which is very conservative and does not allow radical changes, which may need the consensus of FDA, EMEA, Swissmedic. For this reason, maybe an International PhD program certified by FDA is a solution. It is evident, that the guidance of FDA, EMEA, Swissmedic, i.e. of the respective regulatory authorities is a prerequisite.

For the time being, the "Right, First Time" Academia/Industry Interface Laboratory at RPD Tool AG offers to host excellent PhD students or Postdocs from any University of the world, for a research stay of a minimum of 6 months to get trained using a Right, First Time approach based on F-CAD and the mentioned pre-formulation studies. The Academia/Industry Interface Lab is also ready to host scientists from all over the world, who want to spend a sabbatical leave. Applications should be sent to the corresponding author by e-mail. PhD or Postdoc applicants need to be aware, that only a limited number of applicants can be accepted and that applicants are responsible themselves to look for a grant supporting financially the stay and the education at the Right, First Time Academia/Industry Interface Lab at RPD-Tool AG in Switzerland..

Concerning scale-up and the training of people using equipment for large batch sizes, it is somehow surprising, that only pilots are first trained with simulators to use best the aircraft, which in case of failure is an expensive loss. In case of a large batch size with an expensive drug, the quality of the batch should be "Right, First Time". It should not be too difficult to obtain from the "batch" documentation of existing formulations the "scale-up" transfer function of the specific equipment. Thus, it will be easy to design an "equipment simulator" [38, 39] to train people. In addition, the scale-up exercise should become an easy task.

The book "A New Kind of Science" of Stephen Wolfram [37] needs special attention, as it will revolutionize mathematics in general and bioinformatics in a very specific way in life sciences. The latter is of special interest for the pharmaceutical industry. The important point consists in the fact, that the algorithm (C.A. rules) of Wolfram Sciences takes into account very complicated boundary conditions, which will facilitate the design of the boundary condition of e.g. the lung, which will look different and more complicated than a tablet (see Fig. 17), but will facilitate finding solutions to simulate the practical functioning of such a human organ. Thus, as an outlook, in future, it may be possible to simulate *in-silico* the effect of a specific drug on that organ.

Last, but not least, it is important to be thankful to FDA. keeping in mind, that FDA is not only interested in being an institution to enforce law, but is actively promoting Science and Emerging Technologies supporting in the Strategic Plan for Regulatory Science 8 priority areas, of which the third priority area focuses on Product Manufacturing and Quality [49]. The authors of this paper believe, that the described „Right, First Time" workflow and concept should help to reduce time to market from max. 12 years to max. 6 years.

## 8 Acknowledgements

The corresponding author wants to acknowledge the support of the following personalities and institutions, which lead to a continuous and sustainable development of the Institute of Pharmacy at the University of Basel during his professional time as chairman of the Institute: Federal Councillor Ruth Dreifus; Prof. Gian-Reto Plattner, Senator of the Swiss Federation and ViceRector Research of the University of Basel; Prof. Hans-Rudolf Striebel, Councillor of the Canton of Basel-Stadt; Dr. Peter Schmid, Councillor of the Canton Basel-Country; Prof. Jakob Nüesch, President of the Federal Institute of Technology of Zurich (ETH); Prof. Jean-Claude Badoux, President of ETH Lausanne and President of the Swiss Academy of Engineering Sciences (SATW); Prof. Ambros P. Speiser and Willi Roos, Presidents of SATW; Dr. Daniel Vasella, President of Novartis; Dr. Fritz Gerber and Dr. Franz Humer, Presidents of Roche, Prof. Tadeus Reichstein, Nobel Laureate and former Head of the Institute of Pharmacy at the University of Basel and his former PhD students. Special thanks own my former PhD students in the field of Pharmaceutical Technology for their excellent scientific work, most of them occupying today positions in the pharmaceutical industry. The University of Basel is acknowledged for the construction of the Pharmacenter, providing the necessary laboratory space. The National Science Foundation is acknowledged for Federal Funding. Novartis, Roche and Pfizer (during the time of Dr. Jürgen Werani as CEO of Pfizer Germany), and the GLATT group as well as many SMEs of the Swiss Pharmaceutical Industry for Private Funding. The Department of Pharmaceutical Sciences acknowledges the support by GSIA (Swiss Society of Industrial Pharmacists), pharmaSuisse (Swiss Association of Pharmacists) and SGPhW (Swiss Society of Pharmaceutical Sciences). Last, but not least, special thanks to Helen Winkle and Dr. Ajaz Hussain [4], FDA, visiting the Research Facilities of the Institute of Pharmaceutical Technology at the University of Basel, having been an important event for the University.

As professor emeritus and head of the Institute for Innovation in Industrial Pharmacy, IFIIP GmbH, the corresponding author thanks the partner institutions CINCAP and RPD Tool for the excellent collaboration and the following personalities for fruitful discussions: Dr. Jürg Meier, former CEO Novartis Japan; Dr. Ruedi E. Wäger and Dr. Jürgen Werani.

## *REFERENCES*

[1] Mullard, A. Nature Reviews Drug Discovery 10, 82-85 (2011)
[2] Innovation/Stagnation, Critical Path Opportunities Report and List, FDA 2006, Internet publication
[3] ICH Harmonized Tripartite Guideline: Pharmaceutical Development Q8(R2), Current Step 4 version: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf.
[4] Leuenberger, H.; Lanz, M. Pharmaceutical Powder Technology-from Art to Science: the challenge of FDA's PAT initiative. Adv. Powder Technol. 2005, 16, 1-36.
[5] Schreder, S., Research & Development driven pharmaceutical industry – How will the future look like?, SWISS PHARMA 34, Nr.3 (2012),18-21, to be downloaded from www.ifiip.ch : downloads SWISS PHARMA.
[6] Bonny, J.D., Leuenberger, H. Matrix type controlled release systems II: Percolation effects in non swellable matrices, Pharm. Acta Helv. 68, 25-33 (1993) .
[7] Luginbuehl, R.; Leuenberger, H. Use of percolation theory to interpret water uptake, disintegration time and intrinsic dissolution rate of tablets consisting of binary mixtures. Pharm. Acta. Helv., 69, 127-134 (1994).
[8] Krausbauer, E.; Puchkov, M.; Leuenberger, H. Rational estimation of the optimum amount of non-fibrous disintegrant applying percolation theory for binary fast disintegrating formulation. J. Pharm. Sci. 97(1), 529-541 (2008).
[9] Leuenberger, H. The application of percolation theory in powder technology. Adv. Powder Technol. , 10(4), 323-353 (1999).
[10] Leuenberger, H., Puchkov, M., Leu-Marseiler, R., Bonny, J.D. Leuenberger, M. N., Application of percolation theory and fractal geometry to tablet compaction, in Pharmaceutical Powder Compaction Technology, 2nd edition, Celik, M., editor, Informa Healthcare, New York, London, 2011.
[11] Von Orelli, J, Leuenberger, H., Search for technological reasons to develop a capsule or tablet formulation with respect to wettability and dissolution, Int. J. of pharmaceutics, 287 135-145 (2004)
[12] Von Orelli, J. PhD thesis 2005, Search for technological reasons to develop a capsule or tablet formulation, Faculty of Science, to be downloaded Server University of Basel, see: http://edoc.unibas.ch/diss/DissB_7307
[13] Ruegger, C.E. and Celik, M. Advanced compaction research equipment: Compaction simulators, in Pharmaceutical Powder Compaction Technology, 2nd edition, Celik, M., editor, Informa Healthcare, New York, London, 2011.
[14] Leuenberger, H. Scale-up of granulation processes with reference to process monitoring, Acta Pharmaceutica Technologica, 29 (1983) 274–280, to be downloaded from www.ifiip.ch : "Articles download."
[15] Leuenberger, H., Granulation, New Techniques, Pharm. Acta Helv. 57, Nr.3 (1983) 72-82 to be downloaded from www.ifiip.ch. "Articles download".
[16] Leuenberger, H. Scale-up and Process Robustness of Solid Dosage Forms, to be downloaded from www.ifiip.ch : "Presentations"
[17] Leuenberger, H., Puchkov, M., Continuous manufacturing of oral solid dosage forms, to be downloaded from www.ifiip.ch : "Presentations"
[18] Leuenberger, H.; Leuenberger, M. N.; Puchkov, M. Right First Time: Computer-Aided Scale-up for manufacturing solid dosage forms with a shorter time to market. SWISS PHARMA 2010, 32(7-8), 3-13, to be downloaded from www.ifiip.ch : downloads SWISS PHARMA.
[19] Leuenberger, H.; Leuenberger, M. N.; Puchkov, M. Implementing virtual R & D reality in industry: *In silico* design and testing of solid dosage forms SWISS PHARMA 2009, 31(7-8), 18-24, to be downloaded from www.ifiip.ch : downloads SWISS PHARMA.
[20] Leuenberger, H., Leuenberger, M.N., Puchkov M., Virtual Scale-up of manufacturing solid dosage forms, chapter 17 in M. Levin (editor) Pharmaceutical Process Scale-up, 3rd edition, Informa Healthcare, New York, London, 2011.
[21] Dörr, B., Leuenberger H,.Development of a quasi-continuous granulation line for granules . a concept to avoid scale-up problems in Pre-prints of the 1st European Symposium: Process Technology in Pharmaceutical and Nutritional Sciences (Editor: H.Leuenberger, Basel), ISBN 3-921590-55-8, PARTEC 98, Nürnberg, March 10–12, 1998, p. 247–256, to be downloaded from www.ifiip.ch : "Articles download"
[22] Rehoric – Valer Farfan, L., Ganzheitliche systemische Qualitätsbetrachtung in der Produktion fester Arzneiformen: ein praxisorientiertes Vorgehensmodell anhand der Methoden Prozesssimulation und Multivariaten Datenanalyse, 2006, PhD thesis, University of Basel, Faculty of Science, to be down- Loaded : http://edoc.unibas.ch/diss/DissB_7646
[23] Sukowski, L., NIR based process analytical technology: in-line residual moisture determination for a complete batch inspection of lyophilized end-products, 2009, PhD thesis, University of Basel, Faculty of Science, to be downloaded: http://edoc.unibas.ch/diss/DissB_6601
[24] Werani, J.,Grünberg, M., Ober, Ch., Leuenberger, H. Semicontinuous granulation – the process of choice for the production of pharmaceutical granules? Powder Technology, 140,(2004) 163-168. Special Issue: 1st International Workshop on Granulation, Sheffield, 14.1.-15.1.2003.
[25] Leuenberger, H., Scale-up in the 4th dimension in the field of granulation and drying, Preprints, 7th International Symposium on Agglomeration, Albi, France, 2001, 375-384.
[26] Polymorphism in the Pharmaceutical Industry, R. Hilfiker ed., Wiley-VCH,. Weinheim, ISBN. 3-527-31146-7 (2006).
[27] Leuenberger, H., Becher, W., A Factorial Design for compatibility studies in pre-formulationpre-formulationpre-formulationpre-formulation work. Pharm. Acta. Helv. 50, 88-91 (1975) to be downloaded from www.ifiip.ch : "Articles download".
[28] Harrisson, P., Practically implementing forced degradation studies for the drug product, Presentation held on 7th Annual Forced Degradation for Pharmaceuticals, Berlin, January 2013.
[29] Watermann, K.C. et al., Improved Protocol and Data Analysis for Accelerated Shelf-Life Estimations of Solid Dosage Forms, Pharm. Res. 24, 4, 780-790 (2007).
[30] Carella, A.J. Accelerated Stability Assessment Program for packed Solid Dosage Forms (ASAP), Presentation held on Midwestern Biopharmaceutical Statistics Workshop (MBSC) 2010.
[31] Leuenberger H., Betz, G. Donsmark, M.A.S., Jones D.M., Scale-up in the field of granulation and Drying, in Pharmaceutical Process Scale-up, 3rd edition, Levin, M., editor, Informa Healthcare, New York, London, 2011.
[32] Kimura, G., Design of pharmaceutical tablet formulation for a low water soluble drug; search for the critical concentration of starch based disintegrant applying percolation theory and F-CAD (Formulation- Computer Aided Design), Faculty of Science, University of Basel, 2012, to be downlowded from http://edoc.unibas.ch/diss/DissB_9886
[33] Maneerojpakdee, D.,Saetung, K., PhD students of the University of Mahidol, Bangkok, staying for a research stay (RGJ – PhD program grant) at the Academia/Industry Interface Lab c/o RPD Tool AG of the University of Basel, personal communication, see H. Leuenberger "Galenical Drug-Excipient Screening Program for the Development of Robust *Six-sigma* Quality Tablet Formulations, Presentation at Pharmatrans Sanaq Forum 2013, Basel, May 23/24, 2013, see http:// www.pharmatrans-sanaq.com/, Scientific Forum 2013.
[34] Jetzer, W., Leuenberger, H., Zur Bestimmung der Deckeltendenz von pharmazeutischen Wirk- und Hilfsstoffen, Pharm. Acta Helv.m 59, 2-7 (1984) to be downloaded from www.ifiip.ch : "Articles download".
[35] Puchkov, M., Leuenberger, H., Computer-Aided Design of Pharmaceutical Formulations, F-CAD software and a mathematical concept. Glatt Times, Nr. 31 (2011), 2-6. to be downloaded from www.ifiip.ch : "Articles download".
[36] Krausbauer, E.,"Contributions to a science based expert system", PhD thesis, University of Basel, Faculty of Science, 2009, to be downloaded from http://edoc.unibas.ch/diss/DissB_8879.
[37] Wolfram, S. A New Kind of Science, Champaign, IL, Wolfram Media, 2002, ISBN 1-57955-008-8
[38] Puchkov, M., Leuenberger, H., Virtual Equipment Simulators, VES, Virtual training tools – a video game or more? to be downloaded from www.ifiip.ch: "Presentations download".

[39] Puchkov, M. Leuenberger, H. Virtual Equipment Simulators (VES) in Pharmaceutical production – a novel tool for continuous education and personnel training, to be downloaded from www.ifiip.ch "presentations download".
[40] http://www.cds.caltech.edu/conferences/1997/vecs/tutorial/Examples/Cases/777.htm
[41] Puchkov, M., Leuenberger, H. F-CAD, *Six-sigma* Optimization and Cost Savings,Presentation at Biobreakfast Basel "Leveraging thePower of Informatics"(PriceWaterhouseCoopers), to be downloaded from www.ifiip.ch "presentations download".
[42] Leuenberger,H.,Puchkov, M., How will the Quality by Design Initiative affect Formulation Development And Manufacture? Presentation at R.P. Scherer Workshop, to be downloaded from www.ifiip.ch, "presentations download".
[43] Puchkov, M., Leuenberger, H., Unpublished data, CINCAP LLC, Switzerland.
[44] Schneider, B., "Automated Stability Assessment, an Approach for Rapid Formukation Development, Presentation at SGPhW Pharmalunch Basel, to be downloaded from www.ifiip.ch, "Presentations download".
[45] Harrison, P. AstraZeneca, Accelerated stability studies and prediction of *Six-sigma* Quality ready for the market, presentation at Pharmatrans Sanaq Forum 2013, Basel, May 23/24, 2013, see http:// www.pharmatrans-sanaq.com/, Scientific Forum 2013
[46] Puchkov, M., Tschirky, D. , Leuenberger, H. 3D Cellular Automata in Computer-aided Design of Pharmaceutical Formulations: Mathematical Concept and F-CAD software in "Formulation Tools for Pharmaceutical Development (J. Aguilar editor) Woodhead Publishing Series in Biomedicine, ISBN-13:978-1907568992 to be published 2nd quarter 2013.
[47] Juran, J.M., Juran on Quality by Design. The new steps for planning Quality into Goods and Services, Free Press, ISBN-13: 978-0029166833, 1992.
[48] Kimura, G. Puchkov, M., Leuenberger, H. "An attempt to calculate *in silico* disintegration time of tablets containing mefenamic acid, a low water soluble drug. J. Pharm. Sci, accepted for publication 2013.
[49] "Strategic Plan for Regulatory Science", see Internet publication, FDA (accessed January 2013): http://www.fda.gov/ScienceResearch/ SpecialTopics/RegulatoryScience/ucm267719.htm.

# Amalgam

Amalgam – der bestuntersuchte Werkstoff der restorativen Zahnmedizin

– Prof. Dr. med. dent. K. H. Rateitschak,
Zahnärztliches Institut der Universität Basel

Die unbegründete Angst vor Amalgam

– Prof. Dr. med. dent. J. Wirz,
Zahnärztliches Institut der Universität Basel

**Bestellung**

Bitte senden Sie mir _____ Exemplar(e) SWISS DENT Sonderheft «Amalgam» (DE 12-S/92) **à CHF 50.–** (exkl. MwSt.) plus Versandkosten.

Name/Vorname: _____

Adresse: _____

_____

Datum/Unterschrift: _____

Verlag Dr. Felix Wüst AG
In der Hinterzelg 4, 8700 Küsnacht ZH
Fax 044 918 29 70, felixwuest@bluewin.ch

# Pharmatrans Sanaq AG/IFIIP GmbH: 9th Scientific & Technical Forum 2013

**(For program and on-line registration please visit www.ifiip.ch)**

**Right, First Time Concept & Workflow to reduce Time to Market – Boosting Lean *Six-sigma* Quality Development**

Pharmatrans Sanaq AG Pharmaceuticals, Allschwil, und die IFIIP GmbH, Institute for Innovation in Industrial Pharmacy, Pfeffingen BL, führen am 23. Mai 2013 in Basel das 9th Scientific & Technical Forum durch. Die Veranstaltung, zu der Teilnehmende aus der Pharmazeutischen Industrie von Grossbetrieben aber auch von KMUs, von Vertretern aus Hochschulen und von Ämtern eingeladen sind, wird dem aktuellen Thema «Right, First Time, Concept & Workflow» gewidmet sein. Die Implementierung dieses Konzeptes, welches in der Auto- und Flugzeugindustrie zum Standard gehört, ist dank dem Einsatz der Software F-CAD (Formulation – Computer Aided Design) möglich, welche erlaubt, äusserst kostengünstig, eine Tablettenformulierung für die erste klinische Prüfung mit einer six-sigma Qualität zu erstellen und auf Wirkstofffreisetzung zu prüfen. Unter den Vortragenden befinden sich Vertreter von Actelion Pharmaceuticals, Astra Zeneca, von der CINCAP GmbH, von der IFIIP GmbH, von RPD-Tool AG, von der School of Life Science der FHNW und von der SKAN AG. Zur Kostenreduktion der Entwicklungsarbeit wird auch ein Schwerpunkt auf die Laborautomatisierung gelegt. Das oberste Ziel besteht darin, mit dem neuen Workflow die Entwicklungszeiten zu reduzieren, massiv Kosten zu sparen und gleichzeitig die Qualität der Produkte zu erhöhen. Das vollständige Programm inkl. ein Fax – Anmeldeformular für das Scientific Forum 2013 findet man unter www.pharmatrans-sanaq.com und als Beilage zur Ausgabe SWISS PHARMA 3/2013.

***Contact:***
*Pharmatrans Sanaq AG*
*Birsigstr. 79, CH-4011 Basel*
*Phone: +41 (0)61 225 9000*
*Fax: +41 (0)61 225 9001*
*E-Mail: info@pharmatrans-sanaq.com*
*www.pharmatrans-sanaq.com*

# Pharmazeutische Mikrobiologie: Qualitätssicherung – Monitoring – Betriebshygiene


Dankenswerterweise hat ein kompetenter und engagierter Vertreter des Fachgebiets «Hygiene und pharmazeutische Mikrobiologie» die Initiative ergriffen und ein längst überfälliges Nachfolgewerk zu Prof. Dr. K. H. Wallhäußers Kompendium Praxis der Sterilisation, Desinfektion, Konservierung geschrieben.
Der Autor, Dr. Michael Rieth, schöpft seit Jahren sein Wissen aus der Tätigkeit in einem forschenden deutschen Pharmaunternehmen sowie der ehrenamtlichen Mitarbeit in den Ausschüssen der forschenden Pharmafirmen (VfA e. V.) und der deutschen Bundesoberbehörden. Die dort gewonnenen Erfahrungen sind die Basis für die vom Verlag Wiley-VCH herausgegebene Neuerscheinung Pharmazeutische Mikrobiologie – Qualitätssicherung, Monitoring, Betriebshygiene.
Ohne in verwandte Disziplinen wie die medizinische Mikrobiologie oder die Lebensmitteltechnologie abzuschweifen, konzentriert sich das Buch punktgenau auf die mikrobiologische Problematik im pharmazeutischen Arbeitsbereich und repräsentiert den Stand von Wissenschaft und Technik. Dabei ist besonders herauszustellen, dass die nationalen und internationalen Normen auf diesem Gebiet, wie DIN, das Europäische Arzneibuch und die FDA-Regularien, zeitgemässe Berücksichtigung finden. Die Buchausstattung, die Systematik der Einteilung und das griffige Format erleichtern dem Leser die Einarbeitung bzw. die Aktualisierung seines Wissens.
Die Pharmazeutische Mikrobiologie von Michael Rieth ist eine echte Bereicherung für die Bibliothek der auf diesem Gebiet tätigen Kollegen.

*Prof. Dr. Dietrich Krüger, Schriesheim (D)*

*Pharmazeutische Mikrobiologie*
*Qualitätssicherung, Monitoring, Betriebshygiene*
*Michael Rieth*
*Wiley-VCH, Weinheim 2012*
*XX, 372 Seiten, Hardcover*
*119.– Euro*
*ISBN 978-3-527-33097-4*

# Pharmakologie und Urologie

Prof. em. Dr. med. Dieter Hauri, Küsnacht ZH

***In Küsnacht ZH – am rechten Ufer des Zürichsees – befindet sich das Domizil des Verlags und der Redaktion der Zeitschrift SWISS PHARMA. Einer unserer prominenten Nachbarn in Küsnacht ZH ist ein ehemaliger Interviewpartner unserer Zeitschrift SWISS MED, Prof. Dr. med. Dieter Hauri. «Urologie – Rückblick und Ausblick. Die letzten fünf Jahre brachten entscheidende Veränderungen» war das Thema eines Live-Gesprächs, das wir am 17. Dezember 1991 mit Herrn Professor Hauri, damals Direktor der Urologischen Klinik des Universitätsspitals Zürich, aufzeichnen und publizieren durften (SWISS MED 14, 1992, Nr. 2, S. 6–14). Daran erinnerten wir uns als wir durch einen glücklichen Zufall erfuhren, dass unser ehemaliger Interviewpartner am 19. Mai 2013 seinen 75. Geburtstag feiern wird. Wir wagten eine höfliche Zuschrift an seine Gattin, Frau Elisabeth Hauri, und wurden in der Folge spontan zu «Kaffee und Kuchen» bei diesem überaus sympathischen Ehepaar eingeladen. Das Resultat dieses hocherfreulichen Besuches ist die hier veröffentlichte Übersicht von Herrn Professor Hauri zum Thema «Pharmakologie und Urologie» und das was wir zur Ausschmückung noch an Bildern und Kästen dazugegeben haben.***

## Pharmakologie und Urologie im Laufe der Jahrhunderte – ein Blick zurück

Die fruchtbare Zusammenarbeit zwischen der Pharmakologie und der Urologie war inkonstant; ihre gegenseitigen Interessen verliefen im Laufe der Jahrhunderte ausgesprochen wellenförmig. Der Urologe bot als einer der ältesten Spezialisten in der Geschichte der Medizin seine Dienste der Menschheit an. Nur trug er damals nicht diesen Namen und war weit weg von einem Facharzt im heutigen Verständnis. Er gehörte zur Gruppe der Heiler, die seit dem Altertum – und der griechische Name *cheiron* = *Hand* unterstreicht dies – dem Menschen mit den Händen geholfen haben. Lassen wir die Trepanation und die Beschneidung, welche beide als rituelle Handlungen zu verstehen sind, beiseite, so lagen in den Händen des Chirurgen die Wundversorgung, das Einrenken und Stabilisieren von Knochenbrüchen, Abszessinzision, Ausschneiden von oberflächlichen Geschwüren – und der Blasensteinschnitt.

## Der Blasenstein und die Steinschneider

Der Blasenstein begleitete die Menschheit seit ihren Anfängen. Nur die besten Chirurgen wagten sich daran, denn der Blasensteinschnitt endete bis ins hohe Mittelalter bei einem Drittel der Operierten mit dem Tod. Die Überlebenden hatten zu zwei Dritteln mit Komplikationen wie Urinfisteln, Inkontinenz und Impotenz zu


Zu diesem 2007 im Verlag Hans Huber, Hogrefe AG, Bern, erschienenen Buch von Prof. em. Dr. med. Dieter Hauri vermittelt der Verlag folgende Hinweise: «Erst im 20. Jahrhundert hat sich die Urologie endgültig als eigenständiges Fach aus der Chirurgie herausgelöst. Meilensteine waren dabei einerseits die verfeinerten Methoden der Prostataoperation, andererseits die endoskopischen Untersuchungsmethoden, insbesondere die Zystoskopie. Dieser Band zeichnet die Entwicklung der Urologie in der zweiten Hälfte des 20. Jahrhunderts am Beispiel der Schweizer Urologen nach. Er stützt sich dabei auf die bisher unveröffentlichten Akten der 1945 gegründeten Schweizerischen Gesellschaft für Urologie».
(Verlag Hans Huber, Hogrefe AG, Bern; ISBN 978-3-456-84464-0, 136 S., CHF 49.90, Euro 29.95; www.verlag-hanshuber.com)

rechnen. Ausser Medikamenten aus dem Pflanzenreich standen den Steinschneidern keine anderen Mittel zur Verfügung. Drogen aus der Botanik und Alkohol dienten zur Schmerzbekämpfung. Bis heute ist die Pharmakologie daran gescheitert – oder es fehlte das Interesse daran – Medikamente zur Steinauflösung anzubieten; ein Wunsch der schon die hippokratische Medizin beschäftigt hatte. Bis Anfang Neuzeit waren den Chirurgen die seit dem 12. Jahrhundert gegründeten Universitäten verschlossen. Dort sassen eingebildete und schlecht ausgebildete Doktoren der Medizin – die lediglich auswendig gelernte Lehrsätze deklamierten – die zur Wirklichkeit wenig Bezug hatten und sich gegen die Konkurrenz zu

## Brief an die Redaktion SWISS PHARMA

Elisabeth und Dieter Hauri, seit 1966 glücklich verheiratet. Zur Familie gehören zwei erwachsene Söhne; der eine ist Epidemiologe im Fachgebiet der Medizin, der andere tätig im diplomatischen Dienst. Die nächste Familienzusammenkunft wird wohl auf den 19. Mai 2013 anberaumt sein, dem Tag, an dem Dieter Hauri seinen 75. Geburtstag feiern wird. Elisabeth und Dieter Hauri haben ein Hobby: Südfrankreich. Dort verbringen sie seit langem jeweils einige Monate im Jahr.

PROF. DR. MED. DIETER HAURI
8700 Küsnacht ZH
Grundwiesstr. 16
22. Februar 2013

*Lieber Herr Dr. Wüst,*
*Haben Sie herzlichen Dank für ihren Brief, den Sie an meine Frau gerichtet haben. Ich komme Ihren Anforderungen gerne nach: Bezüglich der offiziellen Daten lege ich Ihnen eine Kopie meines Lebenslaufs bei. Er ist in Englisch abgefasst, was zusehends üblich wurde. Zu etwas Persönlicherem: Ich war begeisterter Chirurg und Urologe, und zwar weil dieser Beruf gleichzeitig zwei Tätigkeiten umfasst: Einerseits das Faszinierende und auch Künstlerische, das dieses Fach in sich trägt, anderseits die Möglichkeit, mit dem Patienten persönlich und «hautnahe» kommunizieren zu können. Ich ging nicht in die Praxis, weil mich der Betrieb einer Klinik schon immer fasziniert hatte und dann auch, weil nur dort Wissenschaft und Forschung zeitlebens möglich sind. Die Spezielgebiete, in die ich mich speziell vertieft habe, waren Urodynamik, Urininkotinenz, der Blasenersatz und die erektile Dysfunktion.*
*Seit Ende 2005 bin ich emeritiert und habe dies keinen Moment bereut. Gesundheitspolitik und Verwaltung haben mich in den letzten Jahren zunehmend verärgert und das Leben schwieriger gestaltet. Seit meinem Rücktritt habe ich den Beruf vollständig quittiert. Zum einen hätte ich mir ein medizinisches Leben ohne Klinik kaum vorstellen können. Des Weiteren kann man Chirurgie nur hundertprozentig verantworten. So habe ich mich auf das Bücherschreiben konzentriert. Die zwei letzten «Werke» gestatte ich mir Ihnen beizulegen. Momentan ist ein weiteres Buch im Entstehen. Es geht darin um die historische Entwicklung von Erkenntnissen und Behandlungsmöglichkeiten der erektilen Dysfunktion, wobei als Vorspann das Wesen und Leben Casanovas geschildert werden.*
*Dies wäre mein chirurgisch-urologisches Leben! Darf ich abschliessend eine Frage anbringen: Existiert noch ein Abdruck der Abschiedsrede von Prof. Maurice E. Müller, einem interessanten und unabhängigen Menschen (SWISS MED 7-8/81)?*

*Mit herzlichem Dank für Ihre Anregung und ebensolchen Grüssen!*

schützen wussten. Der Chirurg lernte sein Handwerk vom Meister. Über Jahrhunderte konnte der Chirurg marginal von der Pharmakologie profitieren. Vom Apotheker erhielt er seine Tinkturen, Salben und Pflaster.

### Ab Mitte des 19. Jahrhunderts: Von den Urologen als Erste aufgenommene, bedeutsame Erneuerungen

Erst ab Mitte des 19. Jahrhunderts gelang dank zweier genialer Männer ein markanter Sprung nach vorwärts. Der eine, Ignaz Philipp Semmelweiss (1818–1865), erkannte als erster den entscheidenden Wert der Antisepsis in der Geburtshilfe und führte eine konsequente Händedesinfektion mit Chlorkalklösung ein. Und Joseph Lister (1827–1912) erreichte dieses Ziel mittels Besprühen von Handschuhen, Operationskleidern und dem gesamten Operationsfeld mit verdünnter Karbolsäure. Typisch für das aufstrebende Fach der Urologie war die dankbare Aufnahme dieser Erneuerungen, im Gegensatz zu den konservativen Chirurgen, die a priori um den Erhalt ihrer Domäne fürchteten. Ungefähr gleichzeitig kamen die Anaesthetika und die Narkosemöglichkeiten mit Lachgas, Aether


Bei diesem Werk handelt es sich um die einzige umfassende Darstellung der Geschichte des Blasensteinleidens und seiner Behandlung in deutscher Sprache. Mehr als 200 farbige Abbildungen machen Medizingeschichte lebendig. Für den geschichtlich interessierten Urologen liegt hier ein anschaulich und spannend geschriebenes historisches Werk vor. Das Steinleiden – ein ständiger Begleiter der Menschen seit Anbeginn der Zeiten – stellt mit dem Blasensteinschnitt eines der ältesten Kapitel der Medizingeschichte dar. Eine Darstellung berühmter Steinschneider und Blasensteinträger rundet das Werk ab. (Springer-Verlag, Berlin-Heidelberg, 2013. ISBN 978-3-642-10811-2, 245 S., CHF 62.50, Euro 49.95 D, Euro 51.35 A; www.springer.com/medicine/urology/book/978-3-642-10811-2)

und Chloroform dazu. Durch diese bahnbrechenden Erneuerungen, an denen die Pharmakologie mitbeteiligt war, errang die Chirurgie gewaltige Erfolge und bestätigte ihren mittlerweile errungenen Eintritt in die Universitäten. Mit der Einführung eines brauchbaren Endoskops durch Maximilian Nitze (1848–1906) in den 1870-er Jahren und der Erfindung der X-Strahlen durch Wilhelm Conrad Röntgen (1845–1923) zwanzig Jahre später, verbunden mit den Möglichkeiten von Kontrastmitteln – beide Methoden erleichterten die urologische Diagnostik entscheidend – war der Start zur Abspaltung der Urologie von der Chirurgie gegeben.

### Die Aera der Sulfonamide, Antibiotika, Tuberkulostatika, Zytostatika

In den folgenden Dekaden profitierten andere Fachbereiche mehr von der Pharmakologie als die Urologie, bis in den 1930-er Jahren die Sulfonamide und zehn Jahre später die Antibiotika auf den Markt gelangten. Die lebensbedrohlichen Zustände bei perioperativen Infektionen, die oft das Operationsresultat zunichte machten oder gar das Operieren nicht gestatteten, waren nicht mehr der Hauptfeind der Urologie, welche oft in infizierten Strukturen zu kämpfen hatte. Auch die kurz anschliessend erfundenen Tuberkulostatika waren für die Urogenitaltuberkulose, die dem Fach und seinen Patienten unglaubliche Schwierigkeiten bot, ein wahrer Segen.
Unter anderem auch mit Hilfe der Antibiotika gelangen der operativen Chirurgie zuvor ungeahnte Fortschritte – bis man in der Metastasenchirurgie an Grenzen stiess; in der Urologie beispielsweise bei den Hodentumoren. Man meinte damals, durch Ausdehnung des operativen Vorgehens in der Entfernung der Lymphknoten im Retroperitoneum, diesen Tumoren, die vornehmlich junge Männer in der Blüte ihres Lebens trafen, Einhalt gebieten zu können – und täuschte sich! Bei einer bestimmten Ausdehnung dieser Metastasen änderte sich am sicheren tödlichen Ausgang nichts. Hier half uns die Pharmakologie ab Mitte der 1970-er Jahre mit den ersten wirksamen Zytostatika, die diesen Männern in sehr hohem Prozentsatz eine Heilung versprechen konnten.

### Die Prostata – ein zentrales Problem für den Mann

Ein zentrales Problem für den Mann bedeutet die Prostata. Etwa 30% aller Männer um 50 Jahre verspüren diesbezügliche Beschwerden, und diese nehmen mit zunehmendem Alter sprunghaft zu. Mit einer Operation konnte diesen Männern geholfen werden. Das deutliche Älterwerden der Menschen führte zu einem Ansteigen dieser Eingriffe. Sie brachten zwar Erleichterung, bedeuteten aber nebst Operation einen Spitalaufenthalt und gelegentliche, wenn auch nicht häufige Nebenwirkungen. Hier verhalf die Pharmakologie den Patienten Anfang der 1990-er Jahre mit den Alpha-Adrenorzeptorenblockern und den Alpha-Reduktasehemmern in hohem Prozentsatz und mit geringen Nebenwirkungen zu einer deutlichen und lang andauernden Besserung – und der Urologie zu einem Operationseinbruch von mehr als 50% der durchgeführten Eingriffe.

### Viagra®: Spannende Einblicke für die Erektionsphysiologie

Eine weitere Verbesserung der Lebensqualität bedeutete 1996 das Erscheinen von Viagra® (Sildenafil/Phosphodiesterasehemmer/Typ 5) auf dem Markt, was vor allem in der Laienpresse wie ein Blitz einschlug, und denjenigen Urologen, die sich mit der Erektionsphysiologie beschäftigt hatten, spannende Einblicke brachte. Es darf einmal mehr nicht vergessen werden, wie lange es dauern kann von ersten zündenden Gedanken bis zu einem in der Apotheke erhältlichen Medikament. Von der ersten brauchbaren Erkenntnis über die Entstehung einer Erektion bis zum Erscheinen der «blauen Tablette» dauerte es 144 Jahre!

### *About the Autor*

**Curriculum Vitae**

| | |
|---|---|
| Name | Hauri, Dieter, Prof. Dr. med. |
| Date of Birth | 19 May 1938 |
| | University Education in Medicine in Zurich and Paris |
| 1965 | Final Medical Examination of the Swiss Confederation |
| 1966–1970 | Training in visceral and cardiovascular surgery<br>Dept. of Surgery<br>Chairman: Prof. Å. Senning, University Hospital Zurich – Switzerland |
| 1971 | FMH specialist in surgery. Training in urology |
| as of 1971 | Urologic Clinic, University Hospital Zurich – Switzerland<br>Chairman: Prof. G. Mayor |
| 1973 | FMH specialist in urology |
| 1973 | Assistant medical director under Prof. G. Mayor |
| 1974 | 8-month study trip to various urologic clinics in Germany, Austria, Belgium, England, Poland and the United States |
| 1983 | Postdoctoral thesis on postoperative urinary incontinence, its diagnostics and therapy |
| 1983 | Appointed Professor of Urology and Chairman of the Dept. of Urology, Zurich University Hospital – Switzerland |
| 1989 – 1994 | Secretary Swiss Society of Urology |
| 1995/1996 | President Swiss Society of Urology |
| Membership | Swiss Society of Urology<br>German Society of Urology<br>European Society of Urology<br>International Society of Urology<br>Swiss Society of Surgery<br>International Continence Society<br>Board of Directors of the European Society for Male Genital Surgery (GURS) |
| Honorary Member | Study Group for Experimental Urology of the German Society of Urology<br>Bavarian Union of Urologists<br>Southeast-German Society of Urology<br>Syrian Society of Urology<br>German Society of Urology<br>Swiss Society of Urology |
| Editor | Urologia Internationalis |
| Editorial Board | Archivio Italiano di Urologia/Andrologia |
| Member Scientific Advisory Board | Therapeutische Umschau<br>The European Video J of Urology/European Association of Urology |

**Rückblick – Ausblick**

Es wird weiter gehen und weitere Fortschritte sind absehbar. Und trotzdem lassen sich im Rückblick einschneidende Veränderungen feststellen. Der Fortschrittsglaube und der Optimismus des 20. Jahrhunderts ist Selbstzweifeln und einem gefährlichen Fanatismus gewichen. Auch Selbstgefälligkeit und eine gewisse Gedankenmüdigkeit tragen dazu bei. Es wäre zu wünschen, dass in der Politik und Gesellschaft – ohne Sachkenntnis gesegnet aber mit umso grösserer Hektik agierend – vermehrt eine ruhigere Überlegenheit mit mehr Überblick und gesundem Menschenverstand einkehren möchten.

***Kontakt:***
*Prof. Dr. med. Dieter Hauri*
*Grundwiesstr. 16*
*CH-8700 Küsnacht ZH*
*E-Mail: d-e.hauri@bluewin.ch*

# Belladonna Puzzle – An Application of Mass Spectrometry*

Carina Lämmle and Dr. Rudolf Binder, Bad Saulgau (Germany)

***In the framework of a student project, phytochemicals of the fruits of Atropa belladonna L were studied.***
***The fruit extract was purified by XAD-7 and fractioned by Countercurrent chromatography. The extract and fractions were characterized by HPTLC and HPLC-MSn. For 16 compounds parent ion masses and fragmentation patterns were obtained. 11 compounds were based on petunidin and 5 compounds were based on malvidin. From the fragmentation pattern it is evident that the underlying anthocyanins petunidin and malvidin are glycosylated and acylated. Neutral loss fragments of 308 and 454 were found, suggesting rutinosid and coumaric acid structures. Glucose and/or caffeic acid are likely to be present in all compounds in multiple units. For the main component responsible for the color of the belladonna fruits the structure petunidin-3-O-rutinoside-(p-coumaroyl)-5-O-glucoside or petunidin-3-O-rutinoside (p-coumaroyl)-5-O-caffeosid is proposed. Based on this proposal, the structures of the other observed compounds can be explained by combinations of only a few structural elements. In addition to the colorants, a presumably not previous described hyoscyamine-diglucoside was detected.***

*Keywords: Atropa belladonna L, anthocyanins, alkaloids, Countercurrent chromatography (CCC), mass Spectrometry (MS), petunidin-derivatives, malvidin-derivatives*

## Introduction

In the framework of a student project, the fruits of *Atropa belladonna* L were studied not only with respect to alkaloids, but especially for anthocyanins. Most of the experimental work was performed at the Student Research Center of South Wuerttemberg (SRC©) which provides a platform for student projects with an emphasis on mathematics and science. Moreover, the project was granted essential additional support.
In search for new chemical compounds for medical use and more efficient just as more accurate methods in pharmaceutical research, there is a high interest in the investigation and characterization of ingredients in a variety of fruit and plants. For these reasons, phytochemicals, especially anthocyanins, of *Atropa belladonna L* have been analyzed.
*Atropa belladonna L,* a deadly nightshade and member of the Solanaceae family [Arráez-Román], is mostly found in middle Europe in areas with calcareous soil next to forests.

Prior studies focused on the various tropane alkaloids, primarily hyoscyamine and scopolamine extracted from *Atropa belladonna L leaves,* due to their various pharmacological effects and their pharmaceutical application [Arráez-Román, Christen]. Some alkaloids are already well-established in therapy thanks to anticholinergic and central nervous system activities [Talaty].
Nonetheless, there is little knowledge about the colorants of the *Atropa belladonna L* fruit, the anthocyanins. However, numerous studies on anthocyanins and their aglycones, the anthocyanidins, showed a variety of beneficial actions, e.g. against the initiation and development of vascular diseases. As a common mechanism for a wide variety of effects of flavonoids, including anthocyans, an anti-oxidative action is discussed [Peer].

Aiming at the isolation and identification of anthocyanins, several methods have already been well established. Although not widely used in other fields, Countercurrent chromatography (CCC) seems to be superior to other accustomed methods for the purification of phytochemicals due to its high efficiency and its gentle operation conditions [Ito]. The exceptional method of CCC and the convincing results that were published with manifold applications [Degenhardt, Du] attracted our attention and encouraged us to make use of this method.
First steps in structure elucidation were performed by offline mass spectrometry using a triple-quad instrument (MS-MS) at SRC. The major part of MS, leading to the proposal of structures, however, was done with HPLC-MSn at TU Brauschweig,

## Material and methods

### Reagents

Chemicals used for HPTLC and HPLC were of analytical grade or higher, water was Millipore quality. For extraction and CCC, synthetic grade solvents and deionised water were used as well. Anthocyanins used as reference compounds were purchased from ABCR (Karlsruhe, Germany), anthocyans were from Sigma-Aldrich (St. Louis, MO, USA). Anthocyanins and anthocyanidins were chloride salts.

### Extraction and sample preparation

The fruits of *Atropa belladonna L* were collected in the woods of southern Germany and frozen at -18 °C such as all following samples. For extraction, 1 kg of fruits was homogenized at room temperature with 500 mL water containing 2% of TFA. Filtration yielded 900 mL of crude homogenate.
The total raw homogenate was purified over an Amberlite XAD-7 column (300 x 30 mm), pre-conditioned with 2% TFA in water. The

* Paper presented to the Swiss Society of Pharmaceutical Sciences (SSPhS)/Swiss Academy of Pharmaceutical Sciences (SAPhS), on the occasion of the 5th SWISS PHARMA SCIENCE DAY (SPhSD) 2012, University of Bern, Switzerland, 29 August 2012 (www.sgphw.ch).

homogenate was washed with 1L of water (2% TFA) and eluted with 1L of methanol 10% (2% TFA) followed by 500 mL of methanol 20% (2% TFA). The color fraction was eluted with 250 mL methanol 30% (2% TFA). The eluted fraction was concentrated to a final volume of 50 mL under reduced pressure at 45 °C in a rotary evaporator (Büchi, Heerbrugg, Germany).

**Photometric measurements**
The total anthocyanin content can be roughly determined by using a pH differential method at pH 1 versus pH 4.5 at 510 nm [Fuleki]. For this reason, some crude extract was dissolved in a hydrochloric buffer at pH 1 and an acetate buffer at pH 4.5 and measured at 510 nm with a SPECORD 200 (Analytik Jena, Jena, Germany).

**Countercurrent chromatography (CCC)**
The concentrated extract was further purified and fractioned by means of CCC on a preparative scale. The CCC is a J-type with a synchronous planetary motion. The system consisted of a PU-980 HPLC pump (Jasco, Gross-Umstadt, Germany), a Rheodyne injector equipped with a 5 mL PTFE sample loop, a fraction collector (in-house made) and the Countercurrent chromatograph (LIEBHERR, Ehingen, Germany) itself.
Chromatographic conditions: multilayer coil PTFE tubing (inner diameter 2.3 mm) 280 mL volume (R= 105 mm, r = 55-80 mm, ß = 0.52 – 0.76); modus was head to tail at 700 rpm speed with a flow rate of 1.5 mL/min.
The biphasic aqueous solvent system consisted of methyl-tert-butyl-ether : n-butanol : acetonitrile :water : TFA (1:4:1:5:0.2, v/v) [Du], equilibrated overnight in a separation funnel at room temperature. The coil was pre-filled with upper phase. The injection volume was 5 mL. The fractions were collected in 10 min intervals, pooled according to color and concentrated under reduced pressure resulting in 6 fractions of 10 mL volume each.

**High performance thin layer chromatography (HPTLC) and acidic hydrolysis**
In order to get a first impression of the composition and purity of our raw extract and CCC-fractions, HPTLC was performed on RP-18, w F254-s -plates (Merck, Darmstadt, Germany) using acetonitrile : water : TFA (3:7:0.02, v/v) as a mobile phase. No specific devices were used for HPTLC. Samples were applied by a fine brush, focusing of the bands was accomplished by the high percentage of water in the sample solvent. Acidic hydrolysis was performed on the raw extract and CCC-fractions diluted with water and a final concentration of 25% TFA at 120 °C for 30 min. Hydrolysis products were diluted with 3 volumes of water and applied directly onto HPTLC plates.

**MS-MS**
First MS-MS-experiments were performed on a triple-quad MS (Micromass, Manchester, England) equipped with a electrospray ionization source. The samples were directly introduced via syringe pump and measured in positive mode with ratios 50–1000 m/z. The mass spectrometer operated under following conditions: capillary voltage 3 kV, source temperature 110 °C, cone 30 V. The fragmentation energy differed from 0% for MS up to 35% for MS-MS of the alkaloids.

**HPLC-MSn**
HPLC-MSn was performed on an ion trap Esquire HCT (Bruker Daltonics, Billerica, MA, USA) and HPLC (Agilent, Santa Clara, CA, USA) at TU Braunschweig. HPLC mobile phase consisted of acetonitrile : water : acetic acid with a gradient of increasing acetonitrile percentage. The MS measurements were done in positive as well as negative mode in a range from 100 m/z–3000 m/z. For high intensity peaks, MSn experiments were performed.

## Results and Discussion

**Photometric measurements**
The recovery of colorants in the raw extract from 1 kg of fruits was estimated as approximately 0,5 mmol of total anthocyan dissolved in 50 mL methanol. The calculation was based on an average molar extinction coefficient (epsilon 0) from various reference compounds (see table 1).

| compound | $\lambda_{max}[nm]$ | $\epsilon_0$ |
|---|---|---|
| delphinidin | 538 | 31000 |
| delphinidien 3-O-glucoside | 531 | 32600 |
| cyanidin | 529 | 26300 |
| cyanidin 3-O-glucoside | 522 | 27100 |
| malvidin | 538 | 33600 |
| malvidin 3-O-glucoside | 531 | 28500 |
| malvidin 3,5-O-diglucosid | 531 | n.m. |
| peonidin | 530 | 33800 |
| peonidin 3-O-glucoside | 522 | 28800 |
| pelargonidin | 519 | 31100 |
| pelargonidin 3-O-glucoside | 507 | 32500 |

Table 1: Spectral data of reference compounds dissolved in methanol containing 2% formic acid. Chloride salts of the reference compounds were used. (Note that due to weightings and dilutions the precision and accuracy of epsilon is only 2 to 3 significant digits.)

**High performance thin layer chromatography (HPTLC) and acidic hydrolysis**
Reversed phase HPTLC resolved 1 major and 6 minor colored components (figure 1). The major and 5 of the minor components were more polar than any of the (non-glycosylated) anthocyanins used as references. These components were in a polarity range similar to that of the (3-O-glucosid-) anthocyans but none of them were chromatographically identical to any reference compound used. The least polar trace component was chromatographically similar but not identical to cyanidin. Acidic hydrolysis using TFA converted the major component to the polarity of the least polar component

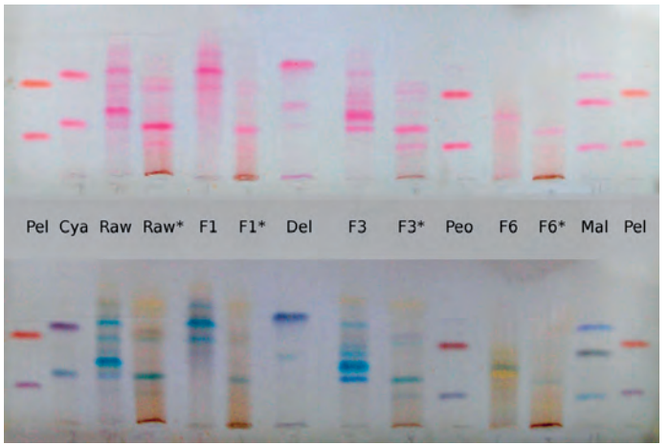



Figure 1: RP-18 HPTLC run (top) and after postchromatographic exposure to NH3 (bottom).
Lanes: Raw: raw extract, F1, F3 and F6: CCC-fractions. *: after acidic hydrolysis.
Pel: Pelargonidin und -3-glucosid, Cya: Cyanidin und -3-glucosid, Del: Delphinidin and -3-glucosid, Peo: Peonidin und -3-glucosid Mal: Malvidin, -3-glucosid and -3,5-diglucosid

and revealed an additional minor component with a polarity similar to peonidin or malvidin (which are not resolved in the chromatographic system used). The major component was clearly enriched in the CCC-fraction 3 (F3 in figure 1).

**MS-Results**

Besides hyoscyamine, a hyoscyamine-derivative with the mass of 614 [M+H]+ was seen in the extract. It exhibited an identical fragmentation pattern as hyoscyamine and 2 additional neutral loss fragments of 162 m/z . The offline MS-measurement of the exact mass of 614.2797 m/z differed only 1.5 mDa from the theoretical mass of hyoscyamine-diglucoside, whereas the deviation to a hypothetical dicaffeosid-derivative was greater than 40 mDa. Thus the proposed structure is hyoscyamine-diglucosid.

The pattern of the belladonna colorants observed in RP-HPTLC was also reflected in RP-HPLC, however with better resolution. In total, more than 20 compounds were seen at 520 nm absorption. The 15 most abundant compounds were evaluated by MSn analysis. A chromatogram of the raw extract is given in figure 2.

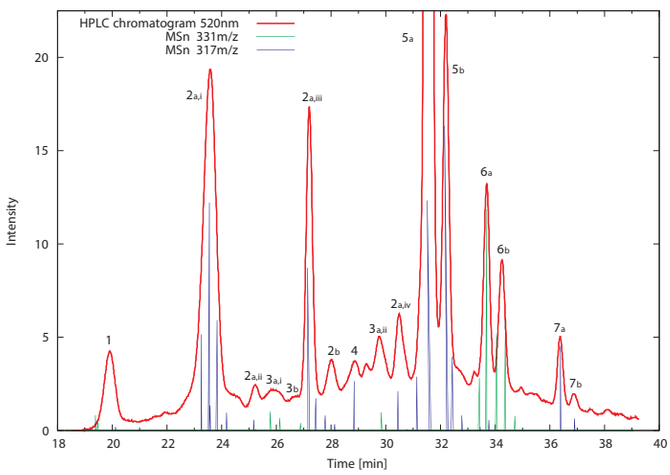



Figure 2: Chromatogram of belladonna raw extract at 520 nm and corresponding MS-fragment scans. Peak numbers were assigned a and b for pairs of peaks with 30 mass units difference and i to iv for peaks with the same mass and fragmentation

Carina Lämmle, winner of the junior science competition "Jugend forscht" in Germany.
At the gymnasium, she attends form 12. In her time off she likes playing piano and tennis. Carina is just 18 years old. Impressively, at the University of Applied Science in Biberach (Oberschwaben, Germany) she is envolved in the workshop "Introduction in mass spectrometry as important tool of instrumental analytics".

In search for the assignment of the chromatographic peaks to anthocyanin, the obtained mass spectra were screened for the mass fragments of common anthocyanins. Only for the fragments 317 m/z [M]+ and 331 m/z [M]+, significant signals have been detected. Thus it is assumed that petunidin and malvidin were the major anthocyanins in the extracts of belladonna fruits. The fragment signals correlated well with the absorption at 520 nm: fragment 317 m/z was present in peaks 1, 2ai 2aii, 2aiii, 2aiv, 2b, 4, 5a, 5b, 7a and 7b, whereas fragment 331 m/z was found in peaks 3a,i, 3aii, 3b, 6a and 6b.
All peaks contained fragments with mass of 308 as well as 162 m/z above the mass of the basic anthocyanin. Pairs of peaks were

| peak number | $[M]^+$ m/z | fragments m/z | 317 pet | 331 mal | + 162 + hex/caff | + 204 + hexAc | + 308 +rut | + 146 +coum | + 176 +fer |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1257 | 1095, 933, 771, 641, 479, 317 | x | - | xxx | - | x | x | - |
| $2_{a,i}$ | 1095 | 933, 771, 641, 479, 317 | x | - | xx | - | x | x | - |
| $2_{a,ii}$ | 1095 | 933, 771, 641, 479, 317 | x | - | xx | - | x | x | - |
| $3_{a,i}$ | 1109 | 947, 785, 655, 493, 331 | - | x | xx | - | x | x | - |
| $3_b$ | 1139 | 975, 815, 655, 493, 331 | - | x | xx | - | x | - | x |
| $2_{a,iii}$ | 1095 | 933, 771, 641, 479, 317 | x | - | xx | - | x | x | - |
| $2_b$ | 1125 | 963, 801, 641, 479, 317 | x | - | xx | - | x | - | x |
| 4 | 949 | 787, 625, 479, 317 | x | - | xx | - | x | - | - |
| $3_{a,ii}$ | 1109 | 947, 785, 655, 493, 331 | - | x | xx | - | x | x | - |
| $2_{a,iv}$ | 1095 | 771, 641, 479, 317 | x | - | xx | - | x | x | - |
| $5_a$ | 933 | 771, 479, 317 | x | - | x | - | x | x | - |
| $5_b$ | 963 | 801,479, 317 | x | - | x | - | x | - | x |
| $6_a$ | 947 | 785, 493, 331 | - | x | x | - | x | x | - |
| $6_b$ | 977 | 815, 493, 331 | - | x | x | - | x | x | x |
| $7_a$ | 975 | 771, 521, 317 | x | - | - | x | x | x | - |
| $7_b$ | 1005 | 801, 521, 317 | x | - | - | x | x | - | x |

Table 2: Peak number, parent ions and fragmentation patterns of belladonna anthocyans. Pet: petunidin, mal: malvidin, hex or caff: hexose or caffeic acid, hexAc: acetylated hexose, rut: rutinose, coum: coumaric acid, fer: ferulic acid.

evident with similar differences in retention time and a mass difference of 30 units. The paired peaks were 2a/2b, 3a/3b, 5a/5b, 6a/6b and 7a/7b. Parent ion mass and fragment patterns are shown in table 2.

Several of the observed parent ion masses and fragmentation patterns have already been described and the underlying compounds were charaterized more detailed in literature. As could be expected, most of the similarities are found within the Solanaceae family. Based on findings of Mes et al., Ando et al. and Zheng et al., structures of the observed belladonna anthocyans can be proposed. From the fragmentation pattern it is evident that the underlying anthocyanins, petunidin and malvidin, are glycosylated and acylated. A neutral loss fragment of 308 m/z and 454 m/z is in accordance with a rutinosid and coumaric acid. Glucose and/or caffeic acid, each corresponding to a neutral loss of 162 m/z, are likely to be present in all compounds from one to three times. The matched pairs of peaks 30 mass units apart can be explained by the interchange of coumaric and ferulic acid. Based on this proposal of structures, a wide variety of the observed compounds can be explained by permutations of very few changes in chemical structure. Figure 3 illustrates the proposed structures.

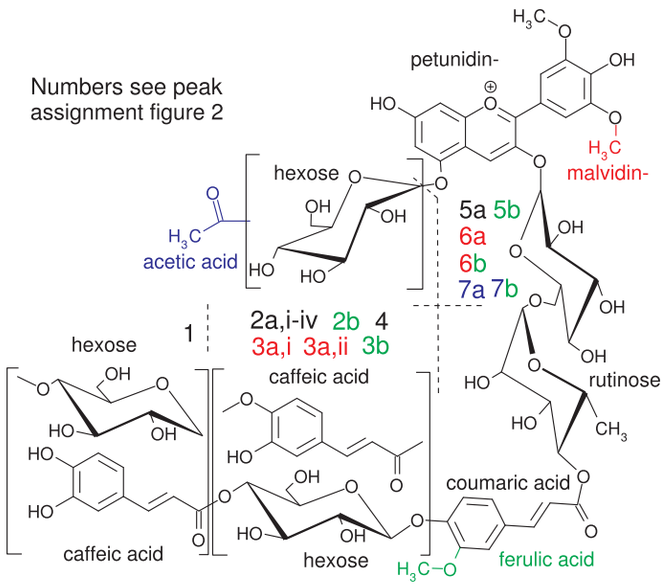



Figure 3: Proposed structure assignment of belladonna anthocyans

Furthermore, the masses 1095 m/z and 1109 m/z appeared in the chromatogram four and two times, respectively, with the same fragmentation pattern, each with a 4 min time shift. There are several possible explanations which we could not resolve. Positional isomerism concerning the glycosidic linkage between the hexoses is discussed [Pourcel]. Moreover, acyl shifts can occur for the caffeoyl-, coumaroyl- or feruloyl- group via an acyl migration mechanism. An exchange from a hexose to a caffeic acid can also not be excluded. In the latter case, the molecules could be differentiated by high resolution mass spectrometry, for the other cases 2D NMR would be a useful tool.

**Acknowledgement**
The presented work was performed as a secondary school student project and was kindly and generously supported by the SRC. Providing know-how, instrumentation and valuable discussions, Prof. P. Winterhalter and especially Dr. G. Jerz (TU Braunschweig, Germany) facilitated the HPLC-MSn measurements which were very skillfully assisted by Ms. M. Rodriguez-Arzaba. They also supported the procurement of a CCC-instrument by lending a model apparatus. In very fruitful discussions, a CCC-instrument was tailored to our needs, manufactured and gratuitously left to us by the apprenticeship workshop at LIEBHERR Ehingen. The project was further supported by Prof. G. Morlock (JLU Gießen, Germany), Prof. R. Süßmuth (TU Berlin, Germany), Prof. G. Schnorrenberg (Boehringer Ingelheim, Biberach, Germany) and others.

**Conclusion**
All anthocyans observed in *Atropa belladonna L* were glycosylated or acylated. The major colorant fraction had a molecular mass of 933 ([M]+) and its fragmentation pattern was consistent with the structure petunidin-3-rut-coum-gluc/caff-gluc/caff-5-gluc. Compounds with higher glycosylation and/or acylation were found as well. Several compounds formed pairs of peaks with 30 mass units difference, potentially indicating an exchange of coumaric acid by ferulic acid. The proposed structures are in line with structures of other fruits or petals published, but are solely concluded from chromatography and mass spectrometry data and thus isomeric structures can not be excluded. The variety and combination of structural elements from belldonnna anthocyans is illustrated in figure 4. Besides the colorants, an hyoscyamine-diglucosid was found in *Atropa belladonna L* fruits.

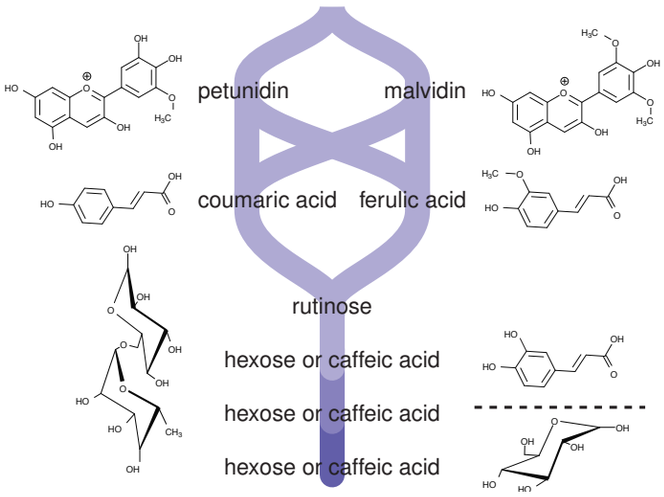



Figure 4: Variety and combination of structural elements from anthocyans of *Atropa belladonna L*

## REFERENCES


- T. Ando, N. Saito, F. Tatsuzawa,T. Kakefuda, K. Yamakage, E. Ohtani, M. Koshi-ishi, Y. Matsusake, H. Kokubun, H. Watanabe, T. Tsukamoto, Y. Ueda, G. Hashimoto, E. Marchesi, K. Asakura, R. Hara, H. Seki. Floral anthocyanins in wild taxa of Petunia (Solanaceae). Biochemical Systematics and Ecology 1999; 27: 623-650.
- D. Arráez-Román, G. Zurek, C. Bäßmann, A. Segura-Carretero, A. Fernández-Gutiérrez. Characterization of *Atropa belladonna L.* Compounds by capillary electrophoresis-electrospray ionization-time of flight mass spectrometry and capillary electrophoresis-electrospray ionization-ion trap-mass spectrometry. Electrophoresis 2008; 29: 2112-2116
- P. Christen. Tropane alkaloids: old drugs used in modern medicine. Elsevier Amsterdam 200; 22: 717–749.
- A. Degenhardt, H. Knapp, P. Winterhalter. Separation and Purification of Anthocyanins by Hight-Speed Countercurrent Chromatography and Screening for Antioxidant Activity. J. Agric. Food Chem. 2000; 48: 338-343.
- Q. Du, G. Jerz, P. Winterhalter. Isolation of two anthocyanin sambubiosides from bilberry (Vaccinium myrtillus) by high-speed counter-current chromatography. J Chromatogr A 2004; 1045: 59-63.

- S. Eichhorn, P. Winterhalter. Anthocyanidins from pigmented potato (Solanum tuberosu) varieties. Food Research International 2005; 38: 943-948.
- T. Fuleki, F. Francis. Quantitative Methods for Anthocyanins. 2. Determination of Total Anthocyanin and Degradation Index for Cranberry Juice. J. Food Science 1968; 33: 78-83.
- Y. Ito, W.D. Conway (Eds). High-Speed Countercurrent Chromatography, Chemical Analysis Series, Vol. 132, Wiley Interscience, New York, 1996, pp. 255–263.
- S. Kim, M. Joo, S. Yoo. Structural identification and antioxidant properties of major anthocyanin extracted from Omija (Schizandra chinensis) fruit. J Food Sci 2009; 74: C134-140.
- P. Mes, P. Boches, J. Myers. Characterization of Tomatoes Expressing Anthocyanin in the Fruit. J. Amer. Soc. Hort. Sci 2008; 133(2): 262-269.
- W. PEER, A. MURPHY, Flavonoids as signal molecules. In: The Science of Flavonoids (Erich Grotewold, ed.) 2006
- L. Pourcel, N. Irani, Y. Lu, K. Riedl, S. Schwartz, E. Grotewold. The Formation of Anthocyanic Vacuolar Inclusions in Arabidopsis thaliana and Implications for the Sequestration of Anthocyanin Pigments. Molecular Plant 2010; 3(1): 78-90.
- N. Talaty, Z. Takáts, R. Cooks. Rapid in situ detection of alkaloids in plant tissue under ambient conditions using desorption electrospray ionization. Analyst 2005; 130: 1624-1633.
- J. Zheng, C. Ding, L. Wang, G. Li, J. Shi, H. Li, H. Wang, Y. Suo. Anthocyanins composition and antioxidant activity of wild Lycium ruthenicum Murr. from Qinghai-Tibet Plateau. Food Chemistry 2011; 126: 859-865.



***Contact:***
*Carina Lämmle and*
*Dr Rudolf Binder*
*Student Research Center*
*South Wuerttemberg (SRC©)*
*Gutenbergstrasse 18*
*D-88348 Bad Saulgau*
*Germany*

*carina.laemmle@sfz-bw.de*

SWISS PHARMA
Swiss Journal of the Pharmaceutical Industry
Schweizerische Zeitschrift für die pharmazeutische Industrie
Revue suisse pour l'industrie pharmaceutique
Rivista svizzera per l'industria farmaceutica

**VERLAG DR. FELIX WÜST AG**
In der Hinterzelg 4
CH-8700 Küsnacht ZH
Telefon 0041 (0)44 918 27 27
Telefax 0041 (0)44 918 29 70
E-Mail felixwuest@bluewin.ch

# Publikationen, 34. Jahrgang, 2012 (Auswahl) (Seite 1 von zwei)

Einzelhefte solange Vorrat: CHF 50.– exkl. MwSt. und zuzüglich Versandkosten

### Pharmaproduktion • Biotherapeutica • Plasmaproteine

1–2/12 CSL Behring – Weltweit führendes Unternehmen im Bereich Plasmaproteine-Biotherpeutika
Im Fokus: Rettung von Menschenleben und die Verbesserung der Lebensqualität von Menschen mit schweren und seltenen Krankheiten
*Gespräch mit:*
*Uwe E. Jocham, Direktionspräsident, CSL Behring AG, Bern*

### Pharmaverpackung • Serialisierung • Fälschungssicherheit • SVI

1–2/12 Quo vadis Pharmaverpackung – am Beispiel der individualisierten Medikation?
– Individualisierung der Medikation als Hebel für eine Verbesserung der Compliance
– Serialisierung: Anforderungen an eine Supply Chain für individualisierte Medikation von der Herstellung bis zum Anwender
– Fälschungssicherheit und Qualitätssicherung: Aspekte beim Herstellen und In-den-Verkehr bringen von individualisierter Medikation
Rückblick auf das 6. SVI Pharma-Verpackungsforum vom 8./9. November 2011 in Basel

### Editorial • Future Scenarios • Strategic Perspectives

3/12 Pharma 2020: Strategic Perspectives
The 2011 GSIA Educational Event of the Swiss Society of Industrial Pharmacists (SSIP)
*Dr. Jürgen Werani, Schuh & Co. Complexity Management Ltd., St.Gallen, Switzerland*

### Megatrends • Foresight • Future Society

3/12 Key Trends Shaping Future Society
*Cornelia Daheim, Managing Partner, Z_punkt The Foresight Company, Cologne (D)*

### Pharmaceuticals • Talent • Future

3/12 The Global Talent Paradox
Recruiting and developing talent in today's global world poses many challenges and opportunities which result in a Global Talent Dilemma.
*Maureen Solero and Claudia Bidwell, Novartis AG, Basel*

### Outsourcing • R&D Productivity • Outlook

3/12 Outsourcing as key success factor for the future of the pharmaceutical industry? The urgently-needed increase in efficiency and productivity requires new business and operating models.
*Antonio M. Russo, Head of Shared Services and Outsourcing Advisory, KPMG Switzerland, Zurich*

### R&D • Pharmaceutical Industry • Future

3/12 Research & Development driven pharmaceutical industry – How will the future look like?
*Dr. Sven Schreder, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss (D)*

### Molecular Diagnostics • Stratified Therapy

3/12 Personalized medicine
A change of strategies
*Prof. Dr. Theodor Dingermann, Goethe University, Frankfurt (D)*

### Operations • Healthcare Leaders • Industry Changes

3/12 Operations for the executive suite: Opening new horizons for current and future healthcare leaders
*Martin Lösch (Stuttgart D), David Keeling (Chicago USA) and Ulf Schrader (Hamburg D), McKinsey & Company*

### Talents • Education • Core Requirements and Competences

3/12 On future challenges of global pharma
What are the core issues, role models and how to find or educate people with the right competencies? A synopsis of the panel discussion.
*Prof. Dr. Gerd Folkers, Department of Chemistry and Applied Biosciences, ETH Zurich and Collegium Helveticum, Zurich*

### Pharmaherstellung • Sterilproduktion • Parenteralia

4/12 F. Hoffmann-La Roche Ltd. in Kaiseraugst: Eines von zukünftig weltweit drei «Roche Center of excellences» für die Sterilproduktion
Ideale Synergieeffekte auf der «Site»: Kombination von Produktion, Hochregallager, Verpackungsbetrieb, Logistik, Qualitätskontrolle und modernster Infrastruktur
*Gespräch mit Dr. Rainer Schmidt, Head of Sterile Drug Manufacturing, F. Hoffmann-La Roche Ltd., Kaiseraugst*

### Logistik • Materialflusskonzept

4/12 Medikamente im sicheren Materialfluss
*Franziska Graf, SSI SCHÄFER AG, Neunkirch SH*

### SVI • Fachgruppe Pharma-Verpackungen

4/12 Zur Geschichte der SVI Fachgruppe Pharma-Verpackungen
Teil. 1: Gründerjahre – Neugründung – Heutige Aktivitäten
*Wolfgang Durrer, Schweizerisches Verpackungsinstitut SVI, Bern*
Teil 2: Verleihung des Pharma-Pack-Awards
*Eugen Sommer, bis 2011 verantwortlicher Programmleiter, SVI Pharma-Verpackungsforum, SVI, Bern*
Teil 3: Wachablösung
*Dr. Felix Wüst, SWISS PHARMA, Küsnacht ZH*

### Pharmaproduktion • Luftzerlegungsanlage

4/12 Aus Luft wird flüssiges Gas – VERISEQ®-Gase für die Pharmaindustrie
Produktion von Flüssiggasen in der Luftzerlegungsanlage Muttenz – spezifische Anforderungen der Pharmaindustrie an die VERISEQ®-Pharmagase
*Maja Studer, Dipl. Lm-Ing. ETHZ, Technischer Kundenservice Industriesegmente Pharmazie, Chemie und Biotechnologie, PanGas, Muttenz*

### Pharmazeutische Lohnverpackung • Lean Production in der Praxis

5/12 Ivers-Lee Schweiz – Innovativer und qualitativ hochstehender Partner für Verpackungslösungen der pharmazeutischen Industrie
Operational Excellence oder der Weg zum prozessorientierten Unternehmen – Nicht nur Verpacker sondern Partner für komplexe Verpackungslösungen
*Gespräch mit Dr. Peter Schüpbach, Geschäftsleiter, Ivers-Lee AG (Burgdorf BE) und Dr. Jürgen Werani, Schuh & Co. Komplexitätsmanagement AG (St. Gallen)*

### Pharmaceutical Production • Sterile Manufacturing • Parenterals

5/12 F. Hoffmann-La Roche Ltd in Kaiseraugst: One of Roche's three future global „Centres of Excellence" for sterile production

SWISS PHARMA
Swiss Journal of the Pharmaceutical Industry
Schweizerische Zeitschrift für die pharmazeutische Industrie
Revue suisse pour l'industrie pharmaceutique
Rivista svizzera per l'industria farmaceutica

**VERLAG DR. FELIX WÜST AG**
In der Hinterzelg 4
CH-8700 Küsnacht ZH
Telefon 0041 (0)44 918 27 27
Telefax 0041 (0)44 918 29 70
E-Mail felixwuest@bluewin.ch

# Publikationen, 34. Jahrgang, 2012 (Auswahl) (Seite 2 von zwei)

Einzelhefte solange Vorrat: CHF 50.– exkl. MwSt. und zuzüglich Versandkosten

Ideal synergy effects at the site:
A combination of production facilities, high-bay warehouse, packaging facility, logistics, quality control and state-of-the-art infrastructure
*A visit to Dr Rainer Schmidt, Head of Sterile Drug Manufacturing, F. Hoffmann-La Roche Ltd, Kaiseraugst*

### Komplexität • Produktion • Leistungsfähigkeit

6/12 Komplexität und deren Konsequenzen für pharmazeutische Produktionsstandorte
Der Einfluss auf die Leistungsfähigkeit und die Rolle von Operational Excellence
*Prof. Dr. Thomas Friedli; Matthias Götzfried, Dipl.-Ing., M.Sc.; Daniel Bellm, Dipl.-Wi.-Ing.; Institut für Technologiemanagement, Universität St.Gallen, St.Gallen*

### Quality by Design • Chemometrics • Pharmacometrics • Econometrics

6/12 Chemometrics, Pharmacometrics and Econometrics: Dimensions of Quality by Design
*Ajaz S. Hussain, Wockhardt USA LLC, Parsippany, NJ, USA*

### Microbiological Enumeration Methods

6/12 Validation of Rapid Microbiological Enumeration Methods: A Case Study within its Regulatory Approach
*Natalia Picioli Gealh, Maringá PR, Brazil*
*Dr. Michael Rieth, Merck Serono, Darmstadt (D)*

### Glasschäden bei Parenteralia • Partikelbildung • Delamination

6/12 Eine spröde Beziehung: Das schwierige Verhältnis der Parenteraliahersteller zu ihrem wichtigsten Packmaterial, dem Glas
*Dr. Thomas Hottiger, Swissmedic, Schweizerisches Heilmittelinstitut, Bern*

### Universität Basel • Juristische Fakultät • Life Sciences-Recht

7–8/12 Life Sciences-Recht an der Juristischen Fakultät der Universität Basel
*Prof. Dr. jur. Dipl.-Biol. Herbert Zech, Universität Basel, Basel*

### Production Pharmaceutique Unité de Séparation des Gaz de l'Air

7–8/12 Des gaz liquéfiés extraits de l'air: la gamme VERISEQ® destinée à l'industrie pharmaceutique
Production de gaz liquéfiés dans l'unité de séparation des gaz de l'air de Muttenz – Les gaz VERISEQ® répondent aux exigences spécifiques de l'industrie pharmaceutique
*Maja Studer, Dipl. Lm-Ing. ETH, Techniques & Services, Segments industriels, Chimie, Pharma, et Biotechnologie, PanGas, Muttenz*

### Spirig Pharma AG • Dermatologika

9/12 Spirig Pharma AG: Seit vielen Jahren unbestrittener Marktleader im Bereich Dermatologie im Pharmamarkt Schweiz
Nach der Ausgliederung der Generikasparte in die Spirig HealthCare AG und deren Verkauf an die STADA Arzneimittel AG setzt die Spirig Pharma AG ihre Wachstumsstrategie in der Dermatologie mit der Suche nach einer strategischen Partnerschaft mit einem multinationalen Player konsequent um
*Gespräch mit Dr. Silvio Inderbitzin, Delegierter des Verwaltungsrates, und mit Dr. Beat Sägesser, CEO, Spirig Pharma AG, Egerkingen*

### Pharmaverpackung • Stickpacks • SVI

9/12 Stickpacks – Die neue Convenience-Verpackung für die Pharmaindustrie
Bericht über den vom Schweizerischen Verpackungsinstitut SVI am 28. August 2012 bei der Firma Invers-Lee AG, Burgdorf, durchgeführten SVI Pharma Roundtable zum Thema «Stickpack- die ideale Portionenverpackung»
*Dr. Peter Schüpbach, Ivers-Lee AG, Burgdorf*
*Prof. Dr.-Ing. Eugen Herzau, Hochschule für Technik, Wirtschaft und Kultur Leipzig, Leipzig (D)*
*O. Becker, Merz Verpackungsmaschinen GmbH, Lich (D)*
*Dr. Georg Kokkinis, Dr. Kokkinis GmbH, Basel*

### Pharmaherstellung • Sterilproduktion • Parenteralia

9/12 Die neue «State of the art» Parenteralia Produktion von Roche in Kaiseraugst: Von der Projektidee zur Realisierung
Die Schweizerische Gesellschaft der Pharmazeutischen Wissenschaften (SGPhW) begrüsste Dr. Rainer Schmidt, Site Head Kaiseraugst, Drug Product Manufacturing, Pharma Technical Operations Biologics, der F. Hoffmann-La Roche Ltd. in Kaiseraugst als Gastreferent an ihrem PharmaLunch vom 28. September 2012
*Gespräch mit Dr. Rainer Schmidt, F. Hoffmann-La Roche Ltd., Kaiseraugst*

### Pharmazeutische Mikrobiologie • CPM-Meeting

9/12 Curriculum für pharmazeutische Mikrobiologie (CPM)
Bericht vom 17. CPM-Meeting in Hoyerhagen/Niedersachsen (D)
*Dr. Michael Rieth, Merck Serono, Darmstadt (D)*

### Swiss Pharma Science Day 2012

10/12 University of Bern, 29 August 2012
Swiss Societey of Pharmaceutical Sciences (SSPhS)
Swiss Academy of Pharmaceutical Sciences (SAPhS)
*Proceedings*
*Conference Report*
*Poster Session – Abstracts P1–P64*
*www.sgphw.ch*

BESTELLSCHEIN
Ich bestelle hiermit folgende Ausgaben der Zeitschrift **Swiss Pharma 2012** zum Preis von CHF 50.– pro Stück (exkl. MwSt. und zuzüglich Versandkosten)

Nr. / / / /

Name, Vorname

Strasse Nr.

PLZ/Ort

Ländercode Datum

Unterschrift

Bitte ausfüllen und einsenden an
**Verlag Dr. Felix Wüst AG, In der Hinterzelg 4,**
**CH-8700 Küsnacht, Telefax 0041 (0)44 918 29 70**
**felixwuest@bluewin.ch**

# SWISS PHARMA: «Mehr als 30 Jahre im Gespräch mit der Pharmazeutischen Industrie der Schweiz» – Live-Interviews der Jahre 1979 bis 2012

Felix Wüst

In unserem Verlag erschien im Gründungsjahr 1979 – neben vier weiteren Titeln – auch die erste Ausgabe der Zeitschrift SWISS PHARMA, Schweizerische Zeitschrift für die pharmazeutische Industrie (ISSN 0251-1673). Der Titel erscheint nunmehr im 35. Jahrgang (2013) und darf trotz Internet weiterhin grossem Interesse begegnen.

Von Anbeginn an haben wir in SWISS PHARMA Live-Interviews mit Spitzenpersönlichkeiten aus der Pharmaindustrie veröffentlicht. Niemand «durfte sich melden». Wir haben ausnahmslos sämtliche Gesprächspartner immer selber ausgewählt. Niemand wurde dafür je honoriert. Alle haben sich ausnahmslos spontan zu den Gesprächen bereit erklärt. Nie hatte es eine Absage gegeben. «Bedingung» für die Interviews war allerdings immer, dass die Gespräche unvorbereitet, eben «full live» stattzufinden hatten. Und so war es, und das war immer ein grossartiges Erlebnis.

Immer wieder erreichten uns Anfragen nach früher erschienenen Interviews, die wir aber leider nicht befriedigend beantworten konnten, war es doch ein Ding der Unmöglichkeit, von allen Heften seit 1979 auch nur 10 oder 20 Exemplare zu lagern. Nun haben wir sämtliche in SWISS PHARMA je erschienenen Interviews mit genauen bibliographischen Angaben aufgelistet (mit Angabe der Seitenzahlen), so dass ein Interessent bei der Zentralbibliothek Zürich bequem und für wenig Geld Fotokopien anfordern kann. Der Verlag stellt ein Verzeichnis aller SWISS PHARMA-Interviews gerne kostenlos in elektronischer Form zur Verfügung. Mit dieser Dokumentation wird auch mitgeteilt, wie man bei der Zentralbibliothek Zürich per E-Mail Fotokopien eines oder mehrerer Interviews anfordern kann. Das ist möglich, weil die Auflistung wie erwähnt jeweils die Seitenzahlen in den betreffenden Heften aufführt, so dass der Interessent exakt jene Druckseiten als Fotokopien anfordern kann, die er benötigt. Die Zentralbibliothek Zürich berechnet sehr vernünftige Preise für diese Fotokopien: Bis zu 20 A4-Seiten pauschal CHF 10.–; jede weitere A4-Seite zu CHF –.50 (50 Rappen). Die Kopien werden per Briefpost und mit Rechnung an den Besteller zugestellt.

Verlag Dr. Felix Wüst AG
E-Mail: felixwuest@bluewin.ch