# What is Life?

## A new Human Model of Life, Disease and Death – a Challenge for Artificial Intelligence and Bioelectric Medicine Specialists

Hans Leuenberger, Orlando FL, USA

*In loving memory of my wife and my parents who passed away too early*

**Summary**

**The publication includes a biographical part, discusses the current Research & Development (R&D) workflow of drug delivery systems and the impact of in-silico design and testing of solid dosage forms. In this context, the current workflow is compared to the workflow of the automotive and aeronautical industry. This discussion leads to the main topic of this publication, to the question «What is life?» This question is discussed in view of searching for new therapies, drugs, biologics, and innovative new technologies, such as bioelectric medicine that were presented at the Lake Nona Impact Forum 2018, see *https://lakenonaimpactforum.org/*. The emerging field of Artificial Intelligence A.I., see *http://www.euro-case.org/index.php/annual-conference/annual-conference-2018.html*, leads to the use of advanced computational science tools such as Formulation Computer Aided Design (F-CAD) and to the «Holy Grail» of modeling a virtual human being who serves as a virtual patient for discovering, developing and testing new therapies. The concept of a virtual human being is based on the idea that each human cell is a microprocessor and the cells of an organ shall closely collaborate to be able to perform coherent decisions and actions similar to a flock of birds using wireless communication. The author presents six axioms that will lead to new research avenues not yet explored. Two of them, axiom 5: «The evolutionary process uses all existing physical laws of the present standard cosmological model to find a niche for a successful survival of the biological system» and axiom 6: «The evolutionary process not only uses all existing physical laws of the present standard cosmological model but beyond to find a niche for a successful survival of the biological system» are of special interest deserving a national research initiative of the format of the US Nano Initiative, see *http://www.wtec.org/loyola/nano/IWGN.Research.Directions*. The axioms are related to the seminal work of Ilya Prigogine, Nobel Laureate in Chemistry in 1977, to the book «Order Out of Chaos, Man's New Dialogue with Nature» and to the ideas he developed with the philosopher Isabelle Stengers, see *https://en.wikipedia.org/wiki/Ilya_Prigogine*. Interestingly, in the latter the laws of processes far from equilibrium that are responsible for the development of life are identical with processes in the socio-economic field. Thus, thanks to A.I. it will be possible to predict the future development of mankind with the hope that the voters in democratic systems will be provided with validated scenarios for finding a sustainable and rational instead of a political solution often based on simple political power play (sppp) being a constant in human history.**

## Prologue

The author thanks Dr Felix Wüst for inviting him to write this article for the 40th anniversary of the journal SWISS PHARMA. The content of this article is based on his seminar at the College of Pharmacy of the University of Florida in Gainesville on November 27, 2018. Thus, the article allows the author to spot on misleading interpretations and explain in more detail the complex topics for the benefit of the readers. He apologizes that it is not possible to shorten the text to such an extent that only an expert will be able to understand the contents. Among others, this article contains topics that are subject to controversial discussion and not part of mainstream research. In such a case this fact is mentioned in the article. The factors governing mainstream research are described in the book «Megatrends – Rise and Fall of Megatrends in Science» Proceedings of CASS-Symposium 2000; editors Margrith Leuthold, Hans Leuenberger and Edward Weibel, Schwabe 2002, see *https://www.amazon.de/Megatrends-Megatrends-Science-Proceedings-CASS-Symposium/dp/3796519393.* For convenience the references are written in italics and directly included in the text.
CASS is the predecessor of the Swiss Academies of Arts and Sciences where Hans Leuenberger was a member of the Board representing the Swiss Academy of Engineering Sciences SATW (https://www.satw.ch/). In 1987, Hans Leuenberger was invited by Prof Werner Richarz, see *https://academictree.org/physics/peopleinfo.php?pid=63647*, to become a member of the Swiss Academy of Engineering Sciences SATW, founded by Prof Heinrich Ursprung *http://www.hls-dhs-dss.ch/textes/d/D31863.php.* Hans Leuenberger served from 1992 to 1996 as president of the SATW Scientific Council and from 1993 to 2001 as executive Vice President of the academy, and as a member of the Board of CASS from 1999 to 2001.

The text of this publication is not subject to a peer review process by scientists representing mainstream research. Thus, the content is the personal opinion of the author. In lieu of the peer review, the author informs the readers that he took the oath after having passed his PhD exam in nuclear physics by the Dean, University of Basel:
***«I now ask you to make a solemn promise and vow; namely that you will always conduct your scientific research honestly and with a full awareness of your responsibilities; that you will consider scientific activity to be a serious obligation, and that – should your future activities put you in a position to serve the cause of science, you will act always with conscientious thoroughness and impartial objectivity».***
This oath is a specific requirement of the faculty of science at the University of Basel and is the dream of Hans Leuenberger that all members of governments (cities, cantons and the Swiss confederation) should take such an oath adapted to their duties for a better world. Thanks to the Swiss system of direct democracy, Switzerland is predestined to be the first country of the United Nations introducing such an oath for politicians.

Prof Heinrich Ursprung, *http://www.hls-dhs-dss.ch/textes/d/D31863.php*, had the great vision of unifying the Swiss Academies of Engineering –, Natural & Medical Sciences, and Humanities. The goal is that the Government of the Swiss Federation shall use this organization as an advisory board for topics of public interest such as issuing the ***«Memorandum on scientific integrity and the handling of misconduct in the scientific context»*** with the reference: *https://www.google.com/search?q=%C2%AB-Memorandum+on+scientific%5B...%5D+integrity+and+the+handling+of+misconduct+in+the+scientific+context&rlz=1C1OKWM_enUS766US766&oq=%C2%ABMemorandum+on+scientific%5B...%5D+integrity+and+the+handling+of+misconduct+in+the+scientific+context&aqs=chrome..69i57.3027j0j7&sourceid=chrome&ie=UTF-8.* This memorandum includes sanctions in the event of misconduct, that is very desirable in the socio-economic field!

## Introduction

The content of this publication is mainly based on information presented at the seminar at the College of Pharmacy of the University of Florida in Gainesville on November 27, 2018, shown in video point, see *http://www.galenusprivatstiftung.at/60.0.html* including the following:

- Biographical part: Study of Nuclear Physics, Research Group Leader at Sandoz, Research and Teaching at the University of Basel including his relations with the Pharmaceutical Industry and with the Journal SWISS PHARMA.
- The R&D workflow of a new Active Pharmaceutical Ingredients (API) for Manufacturing Drug Delivery Vehicles and the Impact of Percolation Theory.
- The workflow of the automotive and aircraft industry using computer aided design for manufacturing vehicles.
- In-silico design of tablets using F-CAD by CINCAP or equivalent.
- Is it possible to create a mathematical model of a virtual patient for testing APIs?
- «What is Life», a new Human Model of Life, Disease and Death as a Virtual Patient.

## Biographical Part

Fig. 1 Paul Huber

### Study of Physics, PhD in Nuclear Physics

Prof Dr Paul Huber (1910-1971), mentor of Hans Leuenberger's PhD thesis was very positive person: His saying was «Von heute an geht es aufwärts!» in English: «From Today Everything Will Be Better!». He was the PhD student of Paul Scherrer at the Federal Institute of Technology in Zurich. As professor emeritus Paul Scherrer gave lectures at the University of Basel, impressing the audience in Basel. Paul Scherrer was supervised by Albert Einstein during his master thesis. Paul Scherrer and Paul Huber were pioneers of Swiss Nuclear Science, see *www.psi.ch & http://academictree.org/physics*. The title of the master thesis of Hans Leuenberger was related to the optimization of a polarized deuteron source: «Intensitätsmessungen an der Quelle polarisierter Deuteronen mit einem Quadrupolmagneten von 10 mm und 6 mm Polschuhabstand». The title of his PhD thesis «Effect of an External Electric Field on the Decay Constant of Tc-99m Halogen Complexes» see *www.ifiip.ch/downloads*, was related to the question, whether technical means exist to reduce the half-life of fission products of radioactive waste. Unfortunately, a change in the decay constant is only possible in the range of less than 0.1 percent. Prof Paul Huber was President of the Board of Surveillance of Radioactivity, KUeR, Switzerland and Hans Leuenberger was his assistant of from 1967 to 1970. Prof Huber was an impressive personality with a high sense of responsibility writing his review of the author's PhD thesis the day before his heart surgery, he did not survive. Prof Paul Huber passed away much too early.
On January 21, 1969, more than 50 years ago, the experimental nuclear plant in the cavern of Lucens suffered from a core melt down, see *https://en.wikipedia.org/wiki/Lucens_reactor.* Hans Leuenberger received filter samples from Lucens to measure it's

radioactivity as head of the α-radiation laboratory of KUeR at the University of Basel.

## Working at Sandoz (today Novartis)

### Sandoz Pharma Inc

Hans Leuenberger was hired by Sandoz Pharma Inc as head of the Drug–Excipient Compatibility Laboratory in the Department of Pharmaceutical Analytical Research and Development in 1971. There, he introduced the use of factorial design as an innovative novel approach to study chemical degradation effects and interactions in pharmaceutical tableting mixtures instead of testing binary drug-excipient systems. After two years he was promoted to research group leader in the Department of Pharmaceutical Research and Development headed by Prof Dr Heinz Sucker. Since Sandoz decided to have a physicist as research group leader for formulating and manufacturing active pharmaceutical substances such as tablets, capsules, etc, they promoted Hans Leuenberger to fill this position. Thus, the tableting process and other unit operations such as the enlargement of powder particles, known as granulation process were a special focus in this field of physical pharmacy. He was responsible for Formulation and Process Technology Research in Solid Dosage Forms.

Fig. 2 Heinz Sucker

### Follow-up Mentors in Industry and at the University of Basel

Prof Dr Heinz Sucker (1928-2014) at Sandoz Inc Basel, was the mentor of the Habilitation Thesis of Hans Leuenberger «Zur Theorie der Pulverkompression», Theory of powder Compression, University of Basel, 1980. Results of this thesis were published with *B D* Rohera, see *Hans Leuenberger* and *B D* Rohera, *Fundamentals of Powder Compression, Pharm. Res. 3, 12-22 & 65-74, 1986*. In 1979 he spent a sabbatical at the University of Michigan, Ann Arbor, USA, being supervised by Prof W I Higuchi, Prof N F Ho, and Prof E N Hiestand as mentors. In 1980, Hans Leuenberger became Head of Pharma R&D, Sandoz at Sarria/Barcelona, Spain ad interim.

### Full time professor in Pharm. Technology at the University of Basel

In 1982 Hans Leuenberger was elected as full time professor and head of the Institute of Pharmacy at the University of Basel, see *SWISS PHARMA 4 (1982) 7-8, p.16*, and *www.ifiip.ch/downloads.* This issue of SWISS PHARMA 1982 and other issues of SWISS PHARMA can be found on the following websites: *http://www.verlag-dr-felix-wuest.ch*, the website of the publisher and *http://www.saphw.ch/de/medien/publikationen*, the website of the Swiss Academy of Pharmaceutical Sciences SAPhW. Hans was warned by friends that the laboratories and the auditorium of the institute are obsolete, located in the historical part of the city of Basel at Totengässlein 3, also hosting the Swiss Museum of Pharmacy, see *https://en.wikipedia.org/wiki/Pharmazie-Historisches_Museum_der_Universit%C3%A4t_Basel.* Before he started lecturing at this institute, Hans Leuenberger received the following gifts from his predecessor, Prof Kurt Leupin: His gown, his gas mask and a rope. The gown fitted very well, but he was surprised to receive a gas mask and the rope. Then, Prof Leupin quickly explained: you need to know, this historical building is very prone to fire-hazards. Thus, the gas mask and rope are a prerequisite to get out of this institute as quickly as possible via the window. Asking about the fate of the students? He just shrugged his shoulders and said that is the responsibility of the government of Basel. As a result, Hans Leuenberger wrote in each annual report to the government, see *www.ifiip.ch/downloads*, that he will not take any responsibility for the lives of the pharmacy students and for the values of the Swiss Museum of Pharmacy at the site of Totengässlein 3. It was a difficult time, having insufficient space for the increasing number of pharmacy students and lacking safety of the laboratories. Once, Beat Fischer, the janitor, had to dispose a burning oil bath through the laboratory window into the schoolyard. Luckily, nobody was in the schoolyard at that time, thus nobody was hurt. It was a difficult time and other institutes also needed more space, and the monetary interest rates were very high.

Thus, it took many years of planning and involvement of the collaborators of Hans Leuenberger, to convince the government of Basel and the parliament to spend 66 Mio Swiss Francs for this building, expecting 10% of subsidies by the Swiss Federal Government. During the critical time Hans Leuenberger served as Dean of the Faculty of Science, University of Basel. He was happy to be advised by Thadeus Reichstein and loved to discuss topics of common interest with him. In 1993, Hans Leuenberger proposed to Reichstein to create the ***Reichstein Medal*** for the purpose to honor personalities, who contributed substantially to the progress in pharmaceutical sciences by their activities. He agreed that the president of the Swiss Society of Pharmaceutical Sciences SGPhW will have the privilege to select the recipients. The first recipient of the Reichstein Medal was Prof Dr William I Higuchi, the mentor of Hans Leuenberger at the University of Michigan in Ann Arbor, see *Basler Zeitung September 29, 1994 p.35*.

Fig. 3 Thadeus Rechstein

### Prof Dr Thadeus Reichstein (1897-1996)

Prof Reichstein was Head of Institute of Pharmacy 1938-1950 at Totengässlein 3, Basel, receiving the Nobel Prize in 1950, see *http://www.nobelprize.org/nobelprizes/medicine/laureates/1950/reichstein-bio.html)*

Thadeus Reichstein played a major role in obtaining the Federal subsidy to construct the new Pharmacenter for hosting the Department of Pharmaceutical Sciences. Due to the closure of the Pharmaceutical Institute In Bern, the number of pharmacy students increased in Basel, which prompted an increase of faculty. The main building of the Pharmacenter (fig. 4) was ready for operation in 2000, see https://www.pharma.unibas.ch.

### The Pharmacenter

Without the great support of the staff, especially of Georg Imanidis, his deputy and Claudia Reinke, chief assistant, and the work of many PhD students discussing and preparing the design of the laboratories for the new building, the pharmacenter, would have never realized, (fig.4). To keep costs of the building under control, careful planning with the architect, Andrea Roost see *http://www.aroost.ch/home.html*) was a prerequisite. In addition, it was necessary to take into account the rising number of pharmacy students, that was experienced annually. This fact resulted in the planning of reserve laboratories included in the lay-out of the future building.

The specialty architect, Dr Jürgen Waibel, Archintegral, 3074 Muri (BE) was hired by the building department of Basel to validate this proposal. The budget and the detailed plans were accepted by the government and the parliament of Basel on June 24, 1992. As a result the reserve laboratories prompted the appetite of other institutes to strengthen their own research in life sciences. This appetite is legitimate but evidently the appetite stimulates the hunger and started to culminate to the point that reports in the local newspaper were questioning whether the new building should really be dedicated to the research and education of pharmacists in Basel. In this context, the research topic «pharmacognosy» became a focus asking whether a roof garden for herbal pharmaceutical plants on this building really makes sense?


Fig, 4: Photomontage of Pharmacenter with Hans Leuenberger and Stefan Winzap, technical assistant, running the formulation laboratories (courtesy Christina Erb, administrative assistant of Pharmaceutical Technology).

Under pressure of the University, the head of the pharmaceutical biology waived his rooftop garden and continued using the greenhouse facilities of Sandoz in Witterswil (Canton of Solothurn). Unfortunately, this decision of the University was not really transparent, since the world famous drug Cyclosporin («Sandimmune») is a natural product, see *https://en.wikipedia.org/wiki/Ciclosporin.*
As a result of these discussions in the local newspaper, on March 9. 1994, the parliament of the city of Basel accepted a resolution with 74 to 0 votes, asking the Federal Government to grant the 10% subsidy allowing the University of Basel to strengthen the research and education of pharmacists in Basel, which is hosting the headquarters of Ciba-Geigy, Sandoz and Roche. The official answer became public and was published in newspapers and periodical such as the *Aerzte Woche, published on Wednesday, March 30, 1994, p.2*, that the Federal Department of Interior plans to concentrate the research and education of pharmacists at the University of Lausanne and Zurich instead, therefore the Pharmacenter at the University of Basel would be closed. This was a new situation for the University of Basel, which is financially supported by the Cantonal governments of Basel (City & County). According to the Swiss Federal Constitution the Cantons are in charge of the Universities and the Swiss Confederation is responsible for the two Federal Institutes of Technology in Lausanne (EPFL) and in Zurich (ETH). This uncertainty impacted the process of realizing the Pharmacenter, and kept politicians very busy see *Hugo Wick, Basler Zeitung, June 1, 1994, p.11*. These discussions in the newspapers are a fundus for conflict researchers. The looming threat, that the School of Pharmacy in Basel will be closed, prompted a top level conference with representatives of the Swiss Academy of Medical Sciences (Werner Stauffacher), the pharmaceutical industry (Georges Haas, Head of Research, Ciba-Geigy), the Federal Government (Heinrich Ursprung, Secretary of State}, the University of Basel (Hans-Joachim Güntherodt, Rector and Werner Arber, Nobel Laureate), the Government of Basel (Hans-Rudolf Striebel) and the Federal Institute of Technology (Jakob Nüesch, President ETH Zurich). The result of this meeting was published on *Thursday, September 29, 1994 in the Basler Zeitung* reporting that the chances for the University of Basel to receive the federal subsidy are intact without confirming that the School of Pharmacy will not be closed. This uncertainty was a constant topic of discussions during the time when the author served as Dean of the Faculty of Science at the University of Basel. Only thanks to the Nobel Laureate Thadeus Reichstein and his former PhD students, and thanks to the strong political leadership of Prof Gian-Reto Plattner, Vice-Rector of the University of Basel and President of the Federal Senate, Prof Hans Rudolf Striebel (Government of Basel-City, Basel), Dr Peter Schmid (Government of Basel-County, Liestal) and Federal Councillor Ruth Dreifuss who granted the Federal subsidy, the School of Pharmacy at the University of Basel was not closed see *Basler Zeitung, April 10, 1996, p.23*. Thus, on *Friday, April, 25, 1997*, the local newspapers *Basler Zeitung and bz* reported the placement of the foundation stone of the Pharmacenter, which contains a confidential message for historians.

**Prof Gian-Reto Plattner**

Hans Leuenberger appreciated the great visions of Gian-Reto Plattner to boost the research in the area of pharmaceutical sciences in the medical city of Basel hosting the headquarters of Novartis and Roche see fig. 5, fig. 6. His idea was to create an alliance between the Department of Pharmaceutical Sciences of the University of Basel and the Life Science Campus of University of Applied Sciences see *https://www.fhnw.ch/en/about-fhnw* in Northwestern Switzerland (FHNW). For this purpose a team of representatives of the University of Basel, the University of Applied Sciences and the pharmaceutical industry was formed leading to a proposal for a close cooperation (see attachment of the annual report of the Institute of Pharmaceutical Technology 2005, see *www.ifip.ch/downloads*. Unfortunately, Hans Leuenberger could not convince the successor of Gian-Reto Plattner as Vice-rector of research to support this promising and visionary project. In 2018 the Life Science Campus of FHNW opened the new building in Muttenz close to Basel see *https://www.fhnw.ch/en/about-fhnw.*

The department of Pharmaceutical Sciences at the University of Basel established a close cooperation with the sister institution at the Federal Institute of Technology (ETH) in Zurich which was called CEPS, Center of Excellence in Pharmaceutical Sciences, see *annual report Institute of Pharm. Technology 1999*, *www.ifiip.ch/downloads.* This organization was headed by Gerd Folkers, see *http://wfcp.ethz.ch/_people/gerd-folkers,* and Hans Leuenberger, CV see *www.ifiip.ch*. During this period the pharmacy students in Basel and in Zurich enjoyed common video lectures in pharmaceutical chemistry. Unfortunately the successor of Gerd Folkers was not interested in the continuation of CEPS.
Consequently, Hans Leuenberger stepped down from his position at the University of Basel in 2006 for founding the start-up companies IFIIP (Institute for Innovation in Industrial Pharmacy) and CINCAP (Center for INnovation in Computer Aided Pharmaceutics) together with Dr Maxim Puchkov, his postdoc from the Mendeleyev University of Chemical Technology of Russia (MUCTR), who received as CEO of CINCAP his Swiss residence. Hans Leuenberger served as Chief Scientific Officer of CINCAP coaching and consulting the CEO who mutated from a chemical engineer to a pharmaceutical technologist. Hans Leuenberger supported the wish of Prof Jörg Huwyler to hire Maxim Puchkov offering him to write a habilitation thesis.

Fortunately, Gian-Reto Plattner as president of the Senate of the Swiss Confederation could convince the Federal Institute of Technology in Zurich (ETH) to open laboratories in Systems Biology forming an alliance between the Biocenter of the University of Basel and the ETH. His initiative boosted the research enthusiasm of the Biocenter today headed by Alexander F Schier, see *https://en.wikipedia.org/wiki/Alexander_F._Schier*, leading to really impressive re-

**View of the Novartis Campus construction in 2006:**

Fig. 5: Novartis was created through a merger of CIBA-GEIGY and Sandoz in 1996.
In reference to the history of Basel the booklet «How Basel changed the world» *www.baselarea.swiss*, *www.merianverlag.ch* is worth to be mentioned.

**View of Roche Tower Nr. 1 in 2017**

Fig. 6: Roche Tower Nr. 1 (178 m) designed by Herzog & de Meuron, architects of the Beijing National Olympic Stadium. Roche Tower Nr. 2 located close to Nr.1 205 m of height will be completed in 2021, *https://www.baselarea.swiss/baselarea-swiss/channels/innovation-report/2018/01/roche-and-novartis-among-most-valuable-companies.html.*

sults among others the findings that the combination of Metformin and Syrosingopine has excellent properties as an anti-cancer agent, see *Syrosingopine sensitizes cancer cells to killing by metformin» M. Hall et al. Science Advances 2, 12, 2016*.

## Career opportunities for PhD students in Pharmaceutical Sciences and Technology

During the time when Hans Leuenberger was chair of Pharmaceutical Technology at the University of Basel the local pharmaceutical industry (Novartis, Roche, Actelion etc) hosted 50% of his PhD students due to lack of University laboratory space. Very many former PhD students in Pharmaceutical Technology were hired by Novartis or Roche following an impressive career among others Andreas Schade in industry and/or academia such as Martin Kuentz. *https://www.fhnw.ch/de/personen/martin-kuentz*. Bhagwan Rohera and Georgios Imanidis were among the first PhD students, following an academic career:
*https://www.stjohns.edu/academics/bio/bhagwan-rohera-phd*
*https://www.fhnw.ch/de/personen/georgios-imanidis*.

Isidoro Caraballo *http://www.us.es/acerca/directorio/ppdi/personal_5761* and Wichan Ketjinda spent a sabbatical leave as PhD students in Basel following an academic career in their countries. Isidoro Carabollo is responsible for the Pharmaceutical Technology at the University of Sevilla and director of the Catedra Iberoamericana-Suiza de Desarrollo de Medicamentos, CISDEM: *http://institucionales.us.es/cisdem/index.php/contacto*. Wichan is an assistant professor at the Prince of Songkla University in Thailand (*https://grad.psu.ac.th/en/faculty-staff/lecturer.html?tid=2469*).

## Cooperation with the Pharmaceutical Industry and institutions world wide

The Department of Pharmaceutical Sciences at the University of Basel is especially attractive for faculty members, postdocs and PhD students due to the opportunities of a close cooperation with the Pharmaceutical Industry in the Medical City of Basel. For optimal teaching and research in pharmaceutical sciences a critical mass of faculty members and infrastructure is needed using the closed loop concept (see fig. 7).

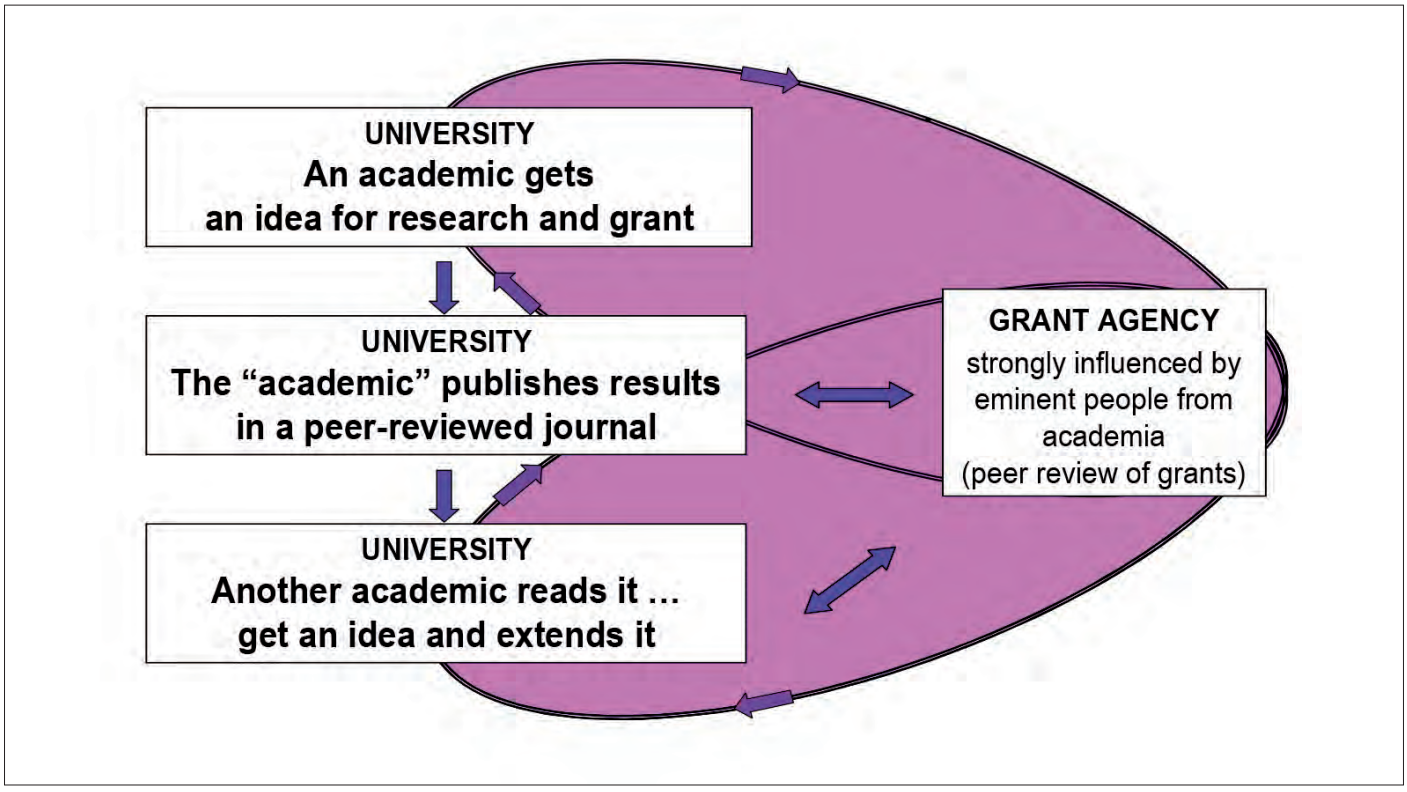



Fig. 7: Standard «Closed Loop Model» of an academic institute having a critical mass.

Due to the lack of space at the University of Basel especially at the former location at the Totengässlein 3, Hans Leuenberger used the open loop concept described in fig.8. Thus, he was hiring scientific experts working at the pharmaceutical industry for part time teaching and for supervising PhD students in industrial laboratories. This concept was a win-win situation for the university and for the industry and academic organizations such as CISDEM, the New Pharmaceutical Technology and Engineering Research Institute in Japan, see *http://sinseizai.com/* and the Ecole des Mines d´Albi-Carmaux, France, see *https://en.wikipedia.org/wiki/%C3%89cole_des_mines_d%27Albi-Carmaux*.
Hans Leuenberger enjoyed giving lectures during a short sabbatical in Albi and signed a cooperation agreement for a double curriculum of a Pharmaceutical PhD & Engineer, see annual report Institute of Pharmaceutical Technology 2006, *www.ifiip.ch/downloads*.

In case of an institute with limited resources the open model is a prerequisite, but any institution should be ready for such a type of cooperation. In this context, the Institute of Pharmaceutical Technology organized with colleagues of CIBA-GEIGY, Sandoz and Roche an event for promoting the idea of cooperation, see *SWISS PHARMA 7 (1985), 6, 25-30*. The Institute of Pharmaceutical Technology had also a close cooperation with the Glatt Group as an equipment manufacturer supplying the global pharmaceutical industry. The Glatt Group obtained 12 patent families and know-how. Soon after Werner Glatt, founder of the Glatt Group, passed away, his successor discontinued the fruitful cooperation.

For promoting the open model, it is important to establish connections to neighboring disciplines such as chemical technology. Hans Leuenberger accepted an invitation by Prof Pavel Sarkisov, president

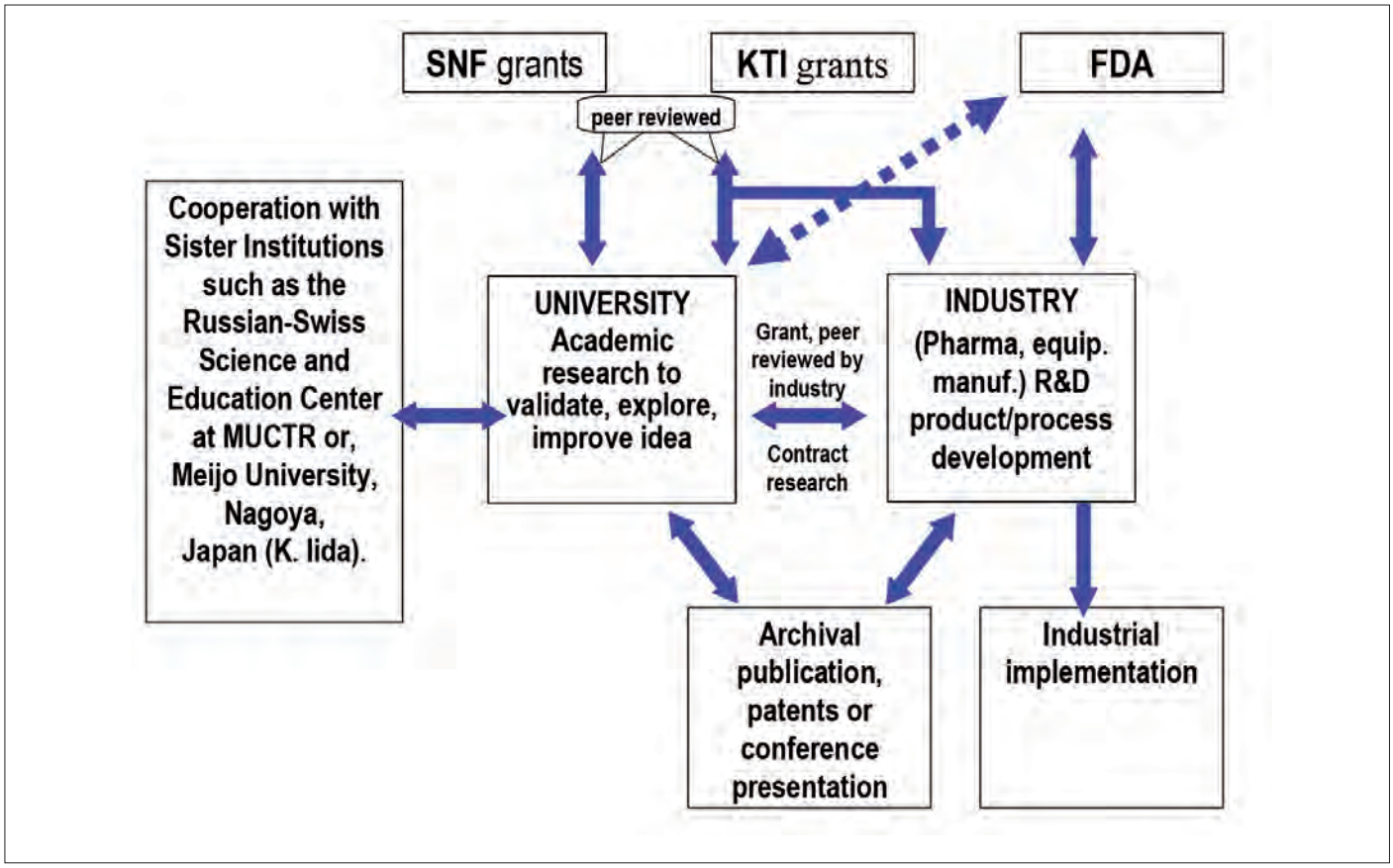



Fig. 8: Open model of an academic institution open for multilateral collaboration.

of the Medeleyev University of Chemical Technology (MUCTR), Moscow, to establish a close cooperation in the area of Pharmaceutical Technology and to establish the Swiss-Russian Laboratory at Tushino. This cooperation was supported by the SCOPES program, see *http://www.snf.ch/en/funding/programmes/scopes/Pages/default.aspx* of the Swiss National Science Foundation, leading to a close cooperation with Prof Natalia Menshutina, Corresponding Member of SATW and SAPhS, *SWISS PHARMA 30 (2008), 7-8, 3-10*. Earlier Hans Leuenberger was invited to lecture the intensive course on «Agglomeration Fundamentals» at the chemical engineering department of the University of Waterloo, Canada, *SWISS PHARMA 7 (1985), 7-8, 11-17*. At the 4th International Symposium on Agglomeration, Toronto, Canada, where he met Yoshiaki Kawashima (Gifu University, Japan), see «Spherical Crystallization as a New Platform for Particle Design Engineering», see *https://www.springer.com/gp/book/9789811367854*. Yoshiaki Kawashima is a Corresponding Member of the Swiss Academy of Pharmaceutical Sciences, SAPhS, see *SWISS PHARMA 30 (2008), 7-8, 3-10*. Interestingly, Hans Leuenberger received most awards from Japan, see about IFIIP, *www.ifiip.ch*, Awards Gallery and the Japanese Society of Powder Technology invited him as a Swiss national to be part of the Japanese committee, organizing the 1996 China-Japan Symposium on Particuology at Tsingua University in Beijing, May 24-25. There he met Prof Mooson Kwauk, who impressed him with his book of *Geometric Mobiles ISBN 7-5025-2087-2 Chemical Industry Press, Beijing* and by his philosophy explaining him that 危机 Wei-Ji = Crisis & Chance, see *Memorial for Mooson Kwauk, www.ifiip.ch/downloads*. Prof Mooson Kwauk was mentor of Prof Jinghai Li, see *http://www.nsfc.gov.cn/english/site_1/news/A1/2018/01-16/65.html*, who are both corresponding members of SATW, see *www.satw.ch*.

In 1985, Hans Leuenberger met Robin Batterham in Toronto and again in 2001 at the 6th World Congress of Chemical Engineering, see *https://chemical.eng.unimelb.edu.au/people/staff.php?person_ID=118440* in Melbourne (23-27 Sept 2001) giving the following presentation: «*Scale-up in the 4th dimension in the field of granulation and drying or how to avoid classical scale-up», Powder Technology 130 (2003) 225 – 230.*

## The Swiss Academy of Pharmaceutical Sciences and SWISS PHARMA

From 1993 - 2001 Hans Leuenberger was Vice President of the Swiss Academy of Engineering Sciences (*www.satw.ch*) and President of its Scientific Council (1992-1996). In 2001-2011, Hans Leuenberger became President of the Swiss Society of Pharmaceutical Sciences. After he stepped down, the society adopted the name of its Scientific Council = Swiss Academy of Pharmaceutical Sciences, see *https://www.saphw.ch/en*. The foundation of the Swiss Academy of Pharmaceutical Sciences in 2008, coincided with the agreement Hans Leuenberger signed with Dr Felix Wüst, editor of the Journal SWISS PHARMA. This document can be found on the webpage of the academy, see *http://www.saphw.ch/de/medien/publikationen* and/or *www.ifiip.ch/downloads* for downloading the *SWISS PHARMA 30 (2008), 7-8, 3-10*.

The idea was to promote the cooperation between the Swiss pharmaceutical industry and academia of the institutions related to teaching and research in pharmaceutical sciences of the Swiss Universities, the Federal Institute of Technology and the Swiss Universities of Applied Sciences. In this context, SWISS PHARMA agreed to publish and distribute a special SWISS PHARMA issue dedicated to the Swiss Pharma Science Day that will be held annually at the University of Bern, the capital of Switzerland. On the other hand, the Swiss Society of Pharmaceutical Sciences agreed that its Scientific Council will prepare a challenging program to attract representatives of the Swiss Pharmaceutical industry to

attend this forum, allowing them to interview faculty members, to hire bachelor, master and/or PhD students, presenting posters with the possibility of obtaining an award, etc. For promoting the idea of the Academy of Pharmaceutical Sciences, the by-laws of the Swiss Society of Pharmaceutical Sciences allowed the Scientific Council to adopt the name of Academy of Pharmaceutical Sciences. Thus, it was possible to carefully select the academicians being Fellows of the Swiss Academy of Pharmaceutical Sciences. In this context, it was decided, that the recipients of the Reichstein Medal become automatically Honorary Members of the Academy. A first list of academicians including foreign and honorary members was published in 2008, see *www.ifiip.ch/downloads*, *SWISS PHARMA 30 (2008), 7-8, 3-10* or http://www.saphw.ch/de/medien/publikationen. Among others, the following were included: Prof Dr Michel Baron, Ecole des Mines Albi-Carmaux, Prof Dr Isidoro Caraballo, University of Sevilla, Prof Dr Ajaz Hussain (formerly FDA), Prof Dr Yoshiaki Kawashima, Aichin Gakuin University, Japan and Prof Dr Natalia V Menshutina, MUCTR, Moscow, Russia.

### PhD Topics in Pharmaceutical Technology

PhD topics in reference to FDA's PAT (Process Analytical Technology) Initiative with the slogan «From Art to Science» became very attractive for the Institute of Pharmaceutical Technology and for the pharmaceutical industry.

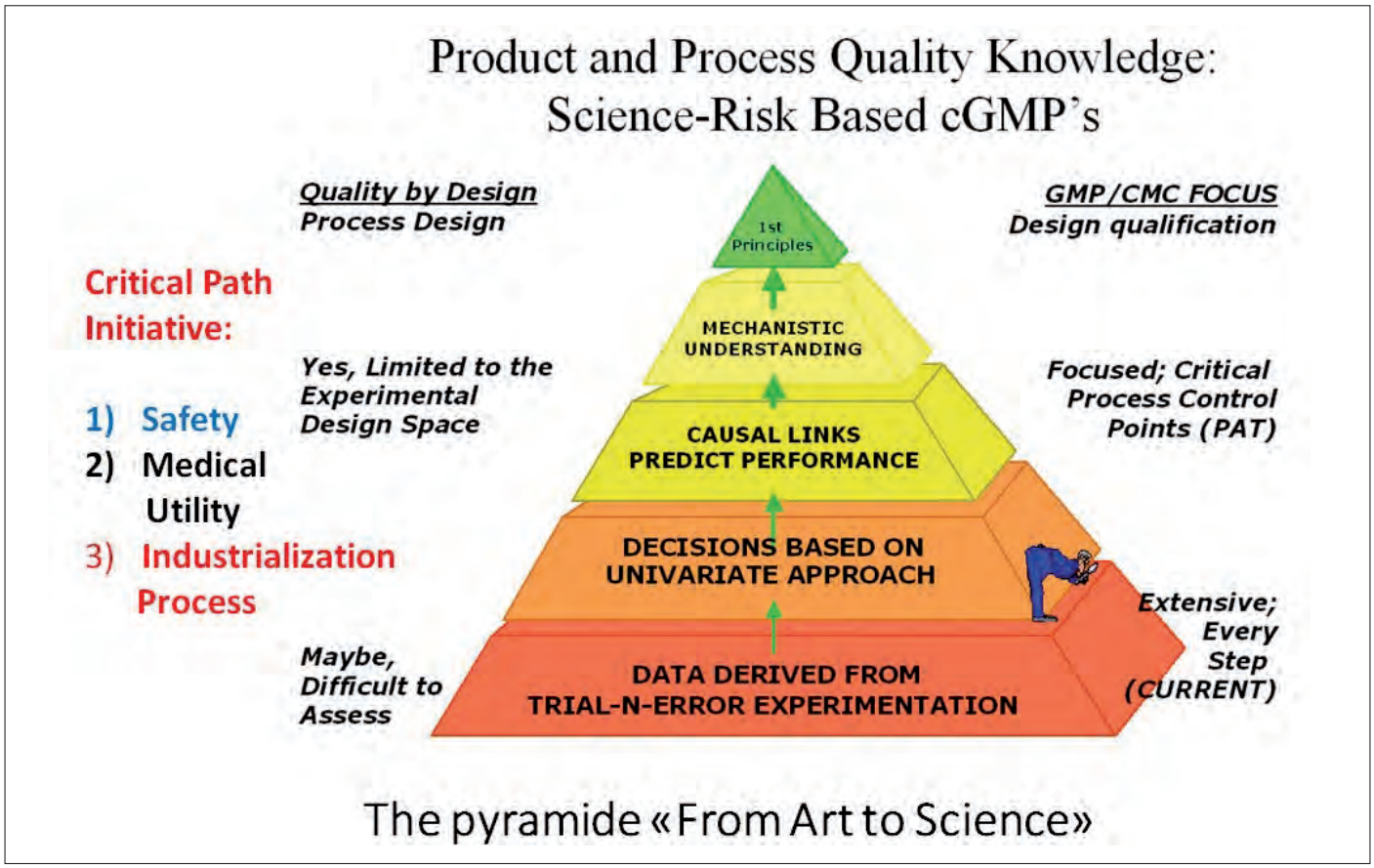



Fig. 9: The pyramid «From Art to Science» is related to the concept of Quality by Design being part of the third dimension of FDA's Critical Path initiative. The average quality of a solid dosage form formulation on the market is two sigma compared to the six sigma world class quality of a computer chip (slide copy, courtesy Ajaz Hussain, FDA).

Many pharmaceutical standard operations such as tableting and size enlargement of fine particles are still poorly understood. Interestingly, pharmaceutical processes often take place far from equilibrium conditions leading sometimes to an important increase in tablet hardness and the disintegration time. This is then reported as an «aging» of a tablet formulation. In a worst case scenario, the aging may be discovered too late that a reformulation is needed and that clinical studies need to be repeated. Thus, the following conclusion can be drawn: «empirical pharmaceutical-technological knowledge» = «art», which needs to be explained. In this context, the question arises: Does it make sense that the research in pharmaceutical technology at the universities is limited to novel drug delivery systems if the conventional drug delivery systems are still poorly understood? The primary goal should be to know more about physical processes far from equilibrium since novel drug delivery systems have the disadvantage, that no «empirical knowledge» is available. Scale-up problems of classical and novel drug delivery systems often causes additional costs. Thus, it is not surprising that the study of Roger S Benson, Jim D J McCabe, Pharm Eng 2004, estimated a worldwide annual loss of $91 bn due to formulation problems, see also Hans Leuenberger in *Pharmaceutical Process Scale-Up, editor Michael Levin, third edition, Informa Healthcare 2011*.

### A rigorous interpretation of the concept «Right, First Time»

«Right, First Time» embraces the principle of quality by design according to fig. 9. A very rigorous interpretation leads to the request that the tablet dosage form for the first Clinical Trials of Clinical Phase 1 should already show market quality. This can only be achieved if the workflow of the automotive and aircraft industry is adopted. In this case, the vehicles, i.e. cars, aircrafts are first designed in-silico, by computer aided design. Indeed, cars and aircrafts are designed and tested in-silico using a computer simulation of a wind channel. This concept can be used for drug delivery vehicles by

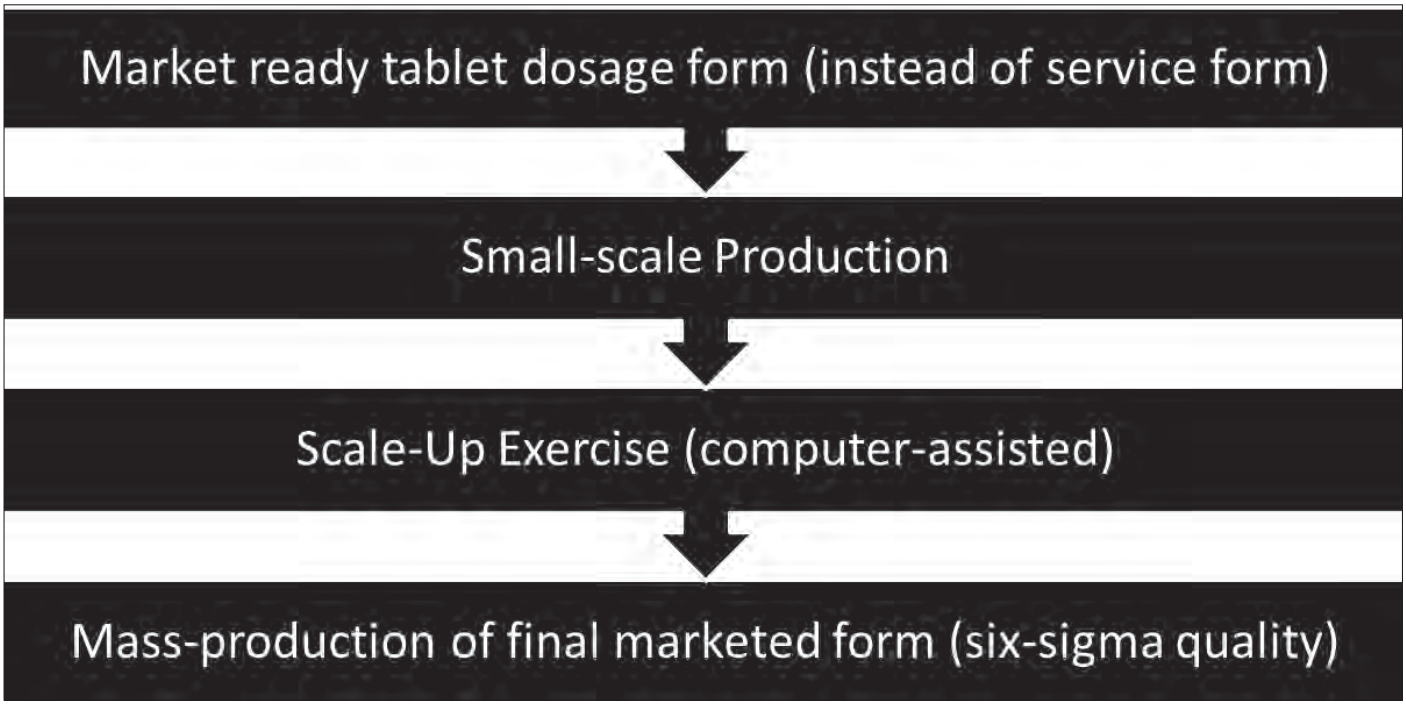



Fig. 10: Rigorous interpretation of the concept «Right, First Time» requests the adoption of the workflow of the automotive and aircraft industry to test a market ready dosage form in Clinical Phase I.

using a formulation computer aided design (F-CAD) and testing the dissolution profile of the active ingredient in-silico, i.e. without using any wet laboratory. Thus, only the optimal formulation needs to be prepared to obtain top quality clinical samples for Clinical Phase 1.

**The impact of a top quality tablet formulation in Clinical Phase I**

The example of a drug substance (broncho dilating theophylline for asthma patients) with a narrow therapeutic range between 10 and 20 µg/ml in the plasma is not unusual: If the plasma concentration in the blood test is lower than 10 µg/ml, the drug will have no effect and if the plasma concentration is higher than 20 µg/ml very toxic side effects may occur (fig.11). Thus, the development of a new active ingredient is immediately stopped, if test persons suffer serious side effects such as grand mal (epileptic attack). In case of a life-saving drug it would be a pity to stop the further development for the benefit of the patients. Such a situation can be avoided with a top quality (six sigma quality like computer chips!) tablet for the first Clinical trials, that the dissolution profile of the new drug substance show a very low variability to be within the therapeutic range.

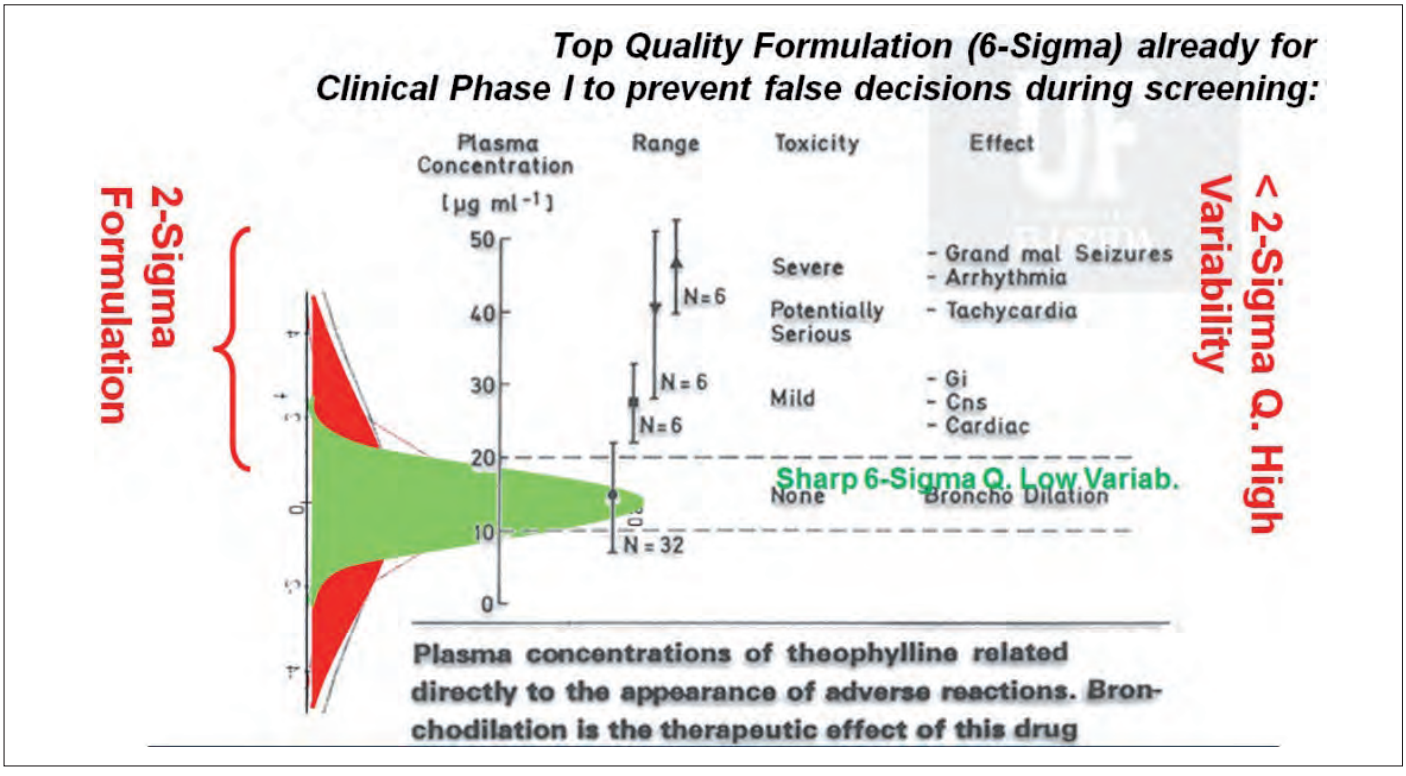



Fig.11: The therapeutic range of the plasma concentration of theophylline is between 10 and 20 µg/ml. Any new active pharmaceutical ingredient needs a six sigma quality of the tablet formulation with a dissolution profile showing a very low variability to be able to define such a narrow therapeutic range.

SWISS PHARMA published a series of contributions to boost this concept, which is capable of reducing time to market and increasing the quality of the tablet formulation:

*Virtual R&D Reality/Proof of Concept, SWISS PHARMA 31(2009), 7-8, 18-29.*

*Right, First Time, Computer – Aided Scale-up, SWISS PHARMA 32,(2010), 7-8, 3-13.*

*Right, First Time, Concept and Workflow, SWISS PHARMA, 35,(2013), 3, 3-16*

see downloads, *www.ifiip.ch/* or *http://www.saphw.ch/de/medien/publikationen*, SWISS PHARMA. It was possible to show that the attrition rate in Clinical Phase I can be reduced using top quality clinical samples, see invited paper: *H Leuenberger and M Leuenberger «Impact of the Digital Revolution on the Future of Formulation Science», European Journal of Pharmaceutical Sciences, 87, 100-111 (2016)*. Elsevier gave permission for a Japanese translation and to publish the English and Japanese versions in Pharm Tech Japan. In this context the following publications were published in English and in Japanese:

*D Maneerojpakdee, A Mitrevej, N Sinchaipanid, J Nowak, H Leuenberger «An Attempt to Adopt the Workflow of the Automotive and Aircraft Industry for the Design of Drug Delivery Vehicles», Pharm Tech (Japan) 33, 2017, 145- 156.*

*K Saeting, G Kimura, A Mitrevej, N Sinchaipanid and H Leuenberger «A systematic pharmaceutical technology drug-excipient screening program for pre-formulation studies» Pharm Tech (Japan) 34, 2018.*

The papers were translated by Go Kimura, a former PhD student of Hans Leuenberger, see *Kimura, Go, 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). 2012, Doctoral Thesis, University of Basel, Faculty of Science. Official URL: http://edoc.unibas.ch/diss/DissB_9886*. Go Kimura introduced the software package F-CAD by CINCAP at the company Shionogi in Japan. Japanese culture is able to integrate advanced technological concepts without neglecting traditional values for a high quality of life. In the framework of the open loop model of fig. 8, Hans Leuenberger accepted scientists from the Pharmaceutical Industry of Japan, who were awarded by their company to spend a sabbatical at the Institute of Pharmaceutical Technology at the University of Basel. His successor Prof Jörg Huwyler continued this tradition: *Reiji Yokoyama, Go Kimura, Christian M. Schlepütz, Jörg Huwyler, and Maxim Puchkov, Modeling of Disintegration and Dissolution Behavior of Mefenamic Acid Formulation Using Numeric Solution of Noyes-Whitney Equation with Cellular Automata on Micro-to-mographic and Algorithmically Generated Surfaces,* see *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6321502/).Pharmaceutics.* 2018 Dec; 10(4): 259.

## Computer Aided Formulation and the Impact of Percolation Theory

The impact of the concept F-CAD (Formulation – Computer Aided Design) and of the Percolation Theory is the focus of the PhD thesis of Go Kimura. In reference to percolation theory see the «*Introduction to Percolation Theory» by Dietrich Stauffer*, free download at: *https://archive.org/details/introductiontope00stau*, and *H. Leuenberger, B D Rohera, & Ch Haas, Percolation Theory – a novel approach to solid dosage form design, Int J of Pharm 38, 1987, 109-115*. Unfortunately, **current official guidelines do not mention the importance of percolation theory and percolation thresholds (= critical concentrations).** In this context see *http://edoc.unibas.ch/diss/DissB_7307 Johannes von Orelli «Search for technological reasons to develop a capsule or a tablet formulation», 2005, PhD Thesis, Basel, see fig.12.*

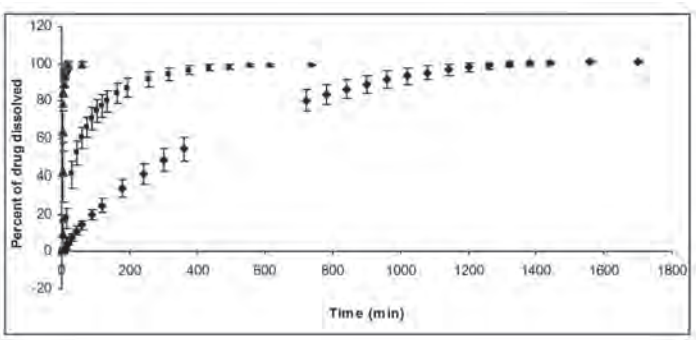



Fig. 12: Problem of a simple capsule formulation based on the principle KISS (Keep it simple and stupid) to avoid high costs regarding the preparation of a top quality of a formulation for Clinical Phase I studies. The amount of drug substance in the plasma (see fig.11) is directly related to the dissollution profile of the drug substance, a pain killer.

The very fast dissolution profile to the left in fig.12 corresponds to a dose of 16 mg of the new hydrophobic drug substance mixed with hydrophilic excipient (lactose), the next dissolution profile to the right was the dissolution profile of a dose of 79 mg mixed with lactose. To keep the size of the capsule constant, 63 mg of drug substance was added to the drug-lactose mixture at the expense of lactose. Since the amount of drug substance in the plasma (fig.11) is directly related to the therapeutic effect, did not show a therapeutic result. Thus, the dose was increased to 111 mg at the expense of the hydrophilic filler lactose. Unfortunately, it took 30 hours until 100% of this drug was released, which is not appropriate for a pain killer that should have an immediate effect.

The different dissolution profiles can be explained on the basis of percolation theory: The 16 mg dose corresponded to a «drug in lactose» mixture (drug concentration below the percolation threshold of ≈ 30 volumetric %) and the 111mg dose corresponded to a «lactose in drug» mixture with a drug concentration above the upper percolation threshold ≈ 70 (100-30) volumetric %. In case of 79 mg dose, both components percolate since the volumetric drug concentration is between 30 and 70%. The existence of a lower and an upper percolation threshold is a **unique property of the three dimensional space.** This property is the reason why life can only exist in 3 (or more than 3!) dimensions leading to the final and so far unpublished part of this article:

## What is life?

Hans Leuenberger asked a friend who studied economics (Dr rer pol) to answer the question «what is life?» a topic discussed in the field of economics: «influence, power and power = money, money, money». In the area of medical, pharmaceutical and physical sciences the answer is not so easy. Since pharmaceutical and medical issues are more complex than physical laws one needs to start with the basic laws of physics.

As already mentioned, **life can only exist in 3D, or > 3D,** since in 3D two different components can percolate simultaneously and a change in the concentration allows a «switch function» which is needed in systems biology. This statement is the formal mathematical-physical proof of Stephan Hawkings idea that in 2D, a digestive tract cannot exist because it would cut the organism in two, i.e. life cannot exist in 2D.

It makes sense that thermodynamics must play an important role, since in a closed system, without an influx of energy any ordered

system degrades according to the second law. This problem of product degradation is well known as «aging», leading to an expiry date of a product. In case of a living system the term «life expectancy» is used for estimating this date. In other words, the «aging» of an ordered system in a closed system leads to chaos. This concept is helpful to develop the contrary = the creation of life. Thus, the system must be open to allow an influx of energy, needed for fueling the «anti-aging process. This concept is described in the book «*Order out of Chaos» of Illya Prigogine,* Nobel Laureate in 1977, see *https://en.wikipedia.org/wiki/Ilya_Prigogine*. An open system with an influx of energy is by definition «far from equilibrium». Such processes are not very well known and often complex due to the nature of biological systems. However it is possible to formulate a set of axioms, conjectures and/or hypotheses that need further studies to be accepted or rejected in the search for the definition of life.

**Axiom 1 (Prigogine)**

**Far from equilibrium conditions exist favoring transformations from disorder into order: Order out of Chaos = Life**

**Creation of Life:**
**Chaos ➡ Order**

Based on axiom 1 the following axiom 2 can be postulated:

**Axiom 2 (Leuenberger)**
**In addition to organic inorganic life must exist:**

Fig. 13: Highly ordered crystalline cubes of Pyrite ($FeS_2$) in nature. Natural crystals such as sapphires, diamonds are a result of a crystallization process far from equilibrium (Axiom 2).

Erwin Schrödinger, co-founder of quantum mechanics, was one of the first scientists, asking the question «What is life?» He defined organic life being a genetic code, see Wikipedia *https://en.wikipedia.org/wiki/What_Is_Life%3F*.

**Axiom 3 (Schrödinger)**
**Life = Information = Software = Our Genetic Code**

**The combination of axiom 1 (Prigogine) with axiom 3 leads to axiom 4**

**Axiom 4 (Schrödinger/ Prigogine)**
**The human being is a living (super) computer**

For initializing life, an open system and energy is needed (axiom 1). For this purpose the evolution invented the fertilization process, the interaction of egg and sperm, and provided that the system receives the necessary energy.

This concept leads to the following conclusion:

**Life = Software and our Body = Hardware**

Expanding the idea:

Each living cell is a microprocessor!

Number of cells in the human body

≈. 37.2 x $10^{12}$ cells!

Without the Microbioms!

**Human Being = a Multiprocessor = a Supercomputer comparable to an Einstein Super Quantum Computer?**

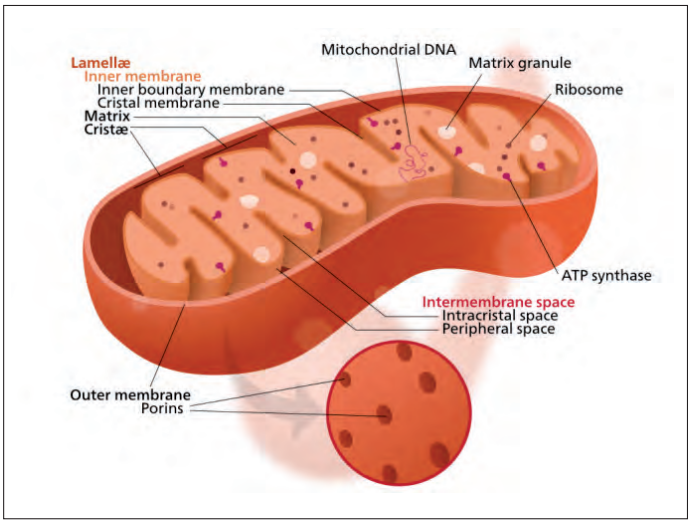
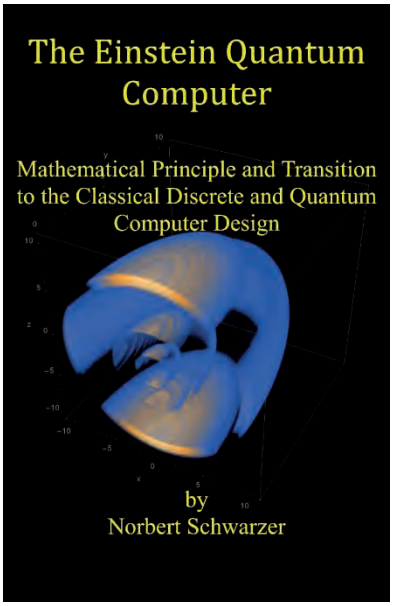



Fig. 14: power supply of the Microprocessor (Mitochondrion, Wikipedia Commons)

**«Life» = «Software», «Body» = «Hardware», Is our body a quantum computer?**




**Thus, or do we need a quantum computer or its advanced version such as an Einstein Quantum Computer to simulate our biological system?**
**In the future, can we use the Einstein Super Quantum Computer to simulate a Virtual Patient projecting a hologram for visualization?**
**This task will be a tremendous challenge for specialists in Artificial Intelligence.**

Fig. 15: Cover page of book by Norbert Schwarzer (courtesy Norbert Schwarzer)

**Axiom 5 (Fröhlich)**
**The evolutionary process uses all existing physical laws of the present standard cosmological model to find a niche for a successful survival of the biological system!**

Thus, quantum mechanical laws must play a vital role and the findings of Herbert Fröhlich are very supportive: In 1978 he published his seminal paper «*Coherent electric vibrations in biological systems and the cancer problem*» *IEEE TRANSACTIONS ON MICROWAVE THEORY AND TECHNIQUES, VOL. MIT-26, NO. 8, AUGUST 1978*.

In his paper, Fröhlich describes a quantum mechanical state in which protein molecules' vibrational modes coalesce at the lowest frequency. This phenomenon is called today a Fröhlich condensation. For this purpose long range phase correlations must exist describing the behavior of such a biological system which is known in the inorganic world in case of superconductors and superfluid liquid helium. These phenomena however occur only at very low temperatures close to -270 °C (= temperature for liquid helium) and are known as Bose-Einstein condensation. In 1987 Georg Bednorz and K Alex Müller, IBM Rüschlikon Laboratories, Zurich, were awarded with the Nobel prize in physics for their discovery of high-temperature ceramic superconductors, showing this macroscopic quantum mechanical effect already at -135 °C. Both mentioned in a seminar at the University of Basel that they prepared and tested numerous mixtures of ceramic cuprates for discovering their first high temperature superconductor Yttrium Barium Copper Oxide ($YBa_2Cu_3O_{7-x}$). Interestingly, they compared their work with the work of a formulator in the pharmaceutical industry.
This macroscopic quantum mechanical (QM) effect is very impressive: see How Quantum Levitation Works & Demo, *https://www.youtube.com/watch?v=8JV9dF6tYr8*.

According to Axiom 2 the superconductivity in the inorganic crystals is the result of the Fröhlich condensation in living tissues. Thus, according to Axiom 5, it makes sense that the evolutionary process takes advantage of the Bose-Einstein condensation at higher temperatures in biological systems.

However, the idea of Herbert Fröhlich is still controversially discussed in literature, but more recent research papers support his findings.

*Jeffrey R. Reimers et al. Weak, strong, and coherent regimes of Fröhlich condensation and their applications to terahertz medicine and quantum consciousness, PNAS _ March 17, 2009 _ vol. 106 _ no. 11 _ 4221-4224, Chemistry.*

*Ida V. Lundholm et al. Terahertz radiation induces non-thermal structural changes associated with Fröhlich condensation in a protein crystal, Struct. Dyn. 2, 054702 (2015); see https://doi.org/10.1063/1.4931825*

*Ilaria Nardecchia et al.,Out-of-equilibrium collective oscillation as phonon condensation in a model protein, see https://arxiv.org/pdf/1705.07975.pdf 23 Jul 2018.*

Interestingly, this most recent work discusses an open system, i.e. that the biomolecule is far from thermal equilibrium with its environment and is subject to an external influx of energy and a simultaneous dissipation due to radiative, dielectric and viscous energy loss. Such a condition is defined in Axiom 1 (Prigogine). The most important point is the fact that Fröhlich condensation and superconductivity exist at higher temperatures showing a type of macroscopic QM effect.

In this context, it is plausible to assume that biology uses entangled photons and/or phonons for a fast non-chemical exchange of information.

**Entanglement of photons** is based on a quantum mechanical effect of ***two polarized photons*****,** *see https://en.wikipedia.org/wiki/Polarization_(waves).* Movies in 3D can be enjoyed thanks to polarized photons using 3D glasses. For simplicity, imagine a barbell consisting of a bar of variable length with rotatable identical spherical plates on each end. The rotatable plates represent the two photons, which rotate at identical ***speed but in opposite direction, where the left photon has a left circular polarization and the right a right circular polarization.*** The bar represents the ***connection*** or the ***entanglement*** between the two particles that can be described as the ***correlation of the rotational direction = polarization.*** Thus, if the direction of rotation of one plate is changed, the other plate changes direction ***at the same time and independent of the length of the bar in between.*** Interestingly, ***this change of direction happens instantly*** even in case the bar length corresponds to the distance between earth and moon. For this reason, this effect corresponds to the ***Einstein Podalsky Roson (EPR) Paradox*** sometimes compared to **telepathy** that happens instantly. Einstein described this effect as a ***«spooky action at distance».*** This ***«spooky» effect is a reality*** and there is an increasing number of publications supporting the existence of entangled photons in nature:

*Lingyan Shi, Enrique J. Galvez & Robert R. Alfano Photon entanglement through brain tissue, Nature Comm (2016), see https://www.nature.com/articles/srep37714.pdf*

*Siyuan Shi, Prem Kumar, Kim Fook Lee Generation of photonic entanglement in green fluorescent proteins, Nature Comm. (2017), see https://phys.org/news/2017-12-quantum-mechanical-effects-biological.html#jCp*

*Ding-Shyue Yang, Peter Baum, and Ahmed H. Zewail, Ultrafast electron crystallography of the cooperative reaction path in vanadium dioxide, Structural Dynamics 3 034304 (2016), see https://aca.scitation.org/doi/pdf/10.1063/1.4953370?class=pdf.*

The third paper deals with an inorganic crystal (see Axiom 2) and not with an organic protein crystal showing a cooperative reaction. Entangled photons are also an important topic in quantum cryptography:

*Thomas Jennewein, Christoph Simon, Gregor Weihs, Harald Weinfurter, and Anton Zeilinger, Quantum Cryptography with Entangled Photons, Phys. Rev. Letters, 84 (2000) 20, 4729-4732.*

It cannot be excluded that the nature of communication used by birds, insects, fish for initiating flocking is the result of entangled photons or phonons. Such a flocking behavior can be modeled using wireless communication between autonomous drones, see

*Gábor Vásárhelyi, Csaba Virágh, Gergő Somorjai, Tamás Nepusz, Agoston E. Eiben and Tamás Vicsek, «Optimized flocking of autonomous drones in confined environments» Science Robotics 3, 20 (2018) http://robotics.sciencemag.org/content/3/20/eaat3536*

Interestingly, the mechanism of a collective «mind» change of flying birds is similar to a cooperative reaction path of a crystalline phase transition in an inorganic material such as vanadium dioxide, see *Structural Dynamics 3 034304 (2016)* supporting Axiom 2 (Leuenberger).

Fig. 16: A swarm-like flock of Starlings, see https://en.13Wikipedia.org/wiki/Flocking behavior

**Axiom 6 (Zwicky)**

**The evolutionary process not only uses all existing physical laws of the present standard cosmological model but beyond to find a niche for a successful survival of the biological system!**

Fig .17: Fritz Zwicky (1898-1974)

The standard cosmological model cannot explain the total mass of the universe, which consists according to Fritz Zwicky mainly of invisible dark matter DM and dark energy DE and only ≈ 4% of the normal visible matter. Thus, only ≈ 4% of the total mass can be explained by the standard cosmological model requesting the existence of all known elementary particles such as electrons, protons, neutrons, neutrinos etc, which could be experimentally detected and validated. However, it was not possible to detect experimentally the hypothetic particles of dark matter such as axions or axion-like particles (wimps). The dark matter can be assumed as an invisible matter of low density filling the space between the planets, stars and galaxies, which are able to attract and focus their DM particles.

It is well known that allergic persons exist being able to detect extremely small amounts of chemicals like a high-tech gas chromatograph. However, there is no proof that persons are sensitive to hypothetical particles of the dark matter. Respecting undisclosed e-mail contacts it can be excluded that axions or wimps are responsible for Melanoma or other types of cancer.

The topic of dark matter particles is controversially discussed, see, Ethan Siegel Forget WIMPs, Axions And MACHOs: Could WIMPzillas Solve The Dark Matter Problem? *https://www.forbes.com/sites/startswithabang/2018/05/09/forget-wimps-axions-and-machos-could-wimpzillas-solve-the-dark-matter-problem/#7e849dfb3a22*

***Being aware that we know ≈ 4% of the total mass we need to be modest.*** It is important to keep in mind that ***Axiom 6 is simply an extension of Axiom 5*** which may become relevant in future knowing more about dark matter and dark energy.

## CONCLUSIONS BASED ON THE SIX AXIOMS

Switzerland hosting world famous Novartis, Roche and many small and medium size pharmaceutical companies should start a National Pharmaceutical Research Initiative of the format of the US Nano Science and Technology Initiative, which took place in Arlington, VA, in 1999, see *http://www.wtec.org/loyola/nano/IWGN.Research.Directions* as a common effort of private and public research institutions. The author was invited by Mihail Roco of NSF,

see *https://en.wikipedia.org/wiki/Mihail_Roco* to participate at this event in 1999, which prompted a world-wide new megatrend of science and technology shaping the future. The root cause for this initiative was the findings of Heinrich Rohrer, (*https://en.wikipedia.org/wiki/Heinrich_Rohrer*) and Gerd Binning at the IBM Laboratories in Rüschlikon ZH, under the direction of Ambros Speiser, president of the Swiss Academy of Engineering Sciences, SATW, see *https://de.wikipedia.org/wiki/Ambros_Speiser*. In 2001 the author suggested a National Research Initiative, see «*Geist und Geld», für einen gemeinsamen Aufbruch in Lehre und Forschung, NZZ July, 24, 2001,* p.12, see *www.ifiip.ch/downloads*. This initiative summarizes visions discussed in the biographical part not implemented in Switzerland. The author received very positive comments from Austria.
The following National Research Initiative is based on the six axioms promoting research in Life Sciences and in Socio-Economics. The latter has the potential to end the schism between Humanities and the Exact Sciences.

## Proposal for a National Research Initiative in Life Sciences

The following research avenues need to be explored:

**Research Topic 1: Human Being = Super (Quantum?) Computer**

**«Body» = Hardware**

The autonomic nerve system is similar to the primary operating system of a human computer. Open question: What is the nature of the non-chemical (wireless?) communication between the microprocessors (cells)? Does this communication correspond to the «refreshing cycle» to keep the computer memory data save?

**The software** capable of modeling a virtual patient based on the concept that the human being is a multiprocessor will be the **ultimate challenge** for Information Technology (IT) and Artificial Intelligence **(AI) specialists** to be hired for such a project. In addition, a **super quantum computer** is required.

**Organic life cannot exist without water** and we still cannot explain all mysteries of water, see
*F N Keutsch and R J Saykally, Water clusters: Untangling the mysteries of the liquid, one molecule a time, PNAS 98 (2001) 10533-10540, and Ph Wernet et al, The structure of the first coordination shell in liquid water, Science, 304, (2004) 995-999.*

**In the field of organic and inorganic life the principle of self-similarity** in reference to shapes, laws, processes and scales is a major topic and **needs to be addressed:** see Benoit Mandelbrot, The Fractal Geometry of Nature, 1982, Fractals and Chaos, 2004. The most important message for life sciences is the ***self-similarity of laws*** governing organic life (**axiom 1**) and inorganic life (**axiom 2**). In addition, axiom 1 needs to be addressed also in the field of ***socio-economics***, see

*Benoit Mandelbrot and Richard L Hudson, The Misbehavior of Markets: A Fractal View of Financial Turbulance, Basic Books, 2006, ISBN-13: 978-0465043576.*

**Hardware failures** can be restored by repairing or replacing the hardware, and by tissue engineering.

**«Life» = Software**
**Options to modify the software** or to modify our life are **limited,** since our initial software is of **genetic origin**. However, our software can be modified by **epigenetics:** environment, food, chemicals, active pharmaceutical ingredients, dark matter(?), photons, elementary particles, physical and mental training, music, meditation etc.
The part of epigenetics deserves special attention in this research project leading to a **convergence of sciences** regarding psychology, psychotherapy, the definition of **consciousness**, the question, whether a robot can be designed showing signs of **consciousness**, the question whether the **mystery of the placebo effect** can be defined as an intrinsic biological «self-healing capacity» being stimulated by our mindset, etc.

**«Disease» = Software and/or Hardware Failure**

**Software Failures** such as human disease due to classical bacterial infection can be «fixed» by antibiotics or using phage therapy. A human viral disease can be treated by immunestimulants or appropriate active pharmaceutical ingredients such as Tamiflu (oseltamivir), etc.
In case of patients suffering from a virus, a bacterial bug and/or a worm the **analogy** between an **infected computer** and a **human being** is evident.

**More complex issues** need specific Active Pharmaceutical Ingredients (API) being able to modify the human computer operating systems correctly.

Since single APIs often show side effects we need more combination products being more specific with less collateral damage, see showcase in the area of cancer chemotherapy such as the combination of Metformin with Syrosingopine:

> «*Syrosingopine sensitizes cancer cells to killing by metformin», M Hall et al, Science Advances 2, 12, Dec.2, 2016.*

Due to the fact that single APIs are capable of intervening into the human «computer operating system», **it is highly recommended to systematically test drug combinations** in view of discovering **more effective treatments with fewer side effects.** In this context, the studies should embrace multiple combinations. In the optimal case the dose of the individual APIs and the side effects can be reduced.

## «The Virtual Patient»

Software to simulate in-silico organs like the human heart, the lungs, the intestinal tract e.t.c. have partially been developed. However, the software for mimicking a holistic virtual patient is still not available and is a major challenge for specialists of Information Technology (IT) and of Artificial Intelligence (AI). In future the virtual patient may be visualized as a hologram for the education of medical doctors (MDs) and pharmacists.

## Research Topic 2: «The Holy Grail» Software

In context with the first research topic, the virtual patient will be used as primary test subject for active pharmaceutical ingredients (APIs) in lieu of a human being. For realizing the «Holy Grail Software» the gaps in fig.18 need to be closed. Thus, it will be possible to achieve a fast secure and reliable workflow for developing, manufacturing and marketing new chemical entities and/or new combinations of known drugs by adopting the workflow of the automotive and aircraft industry (see fig.10). The Research Topic 2 needs to include Nano-Medicine: see *Ref. Müller, B / Van de Voorde, M (eds.) Nanoscience and Nanotechnology for Human Health ISBN: 978-3-527-33860-3*

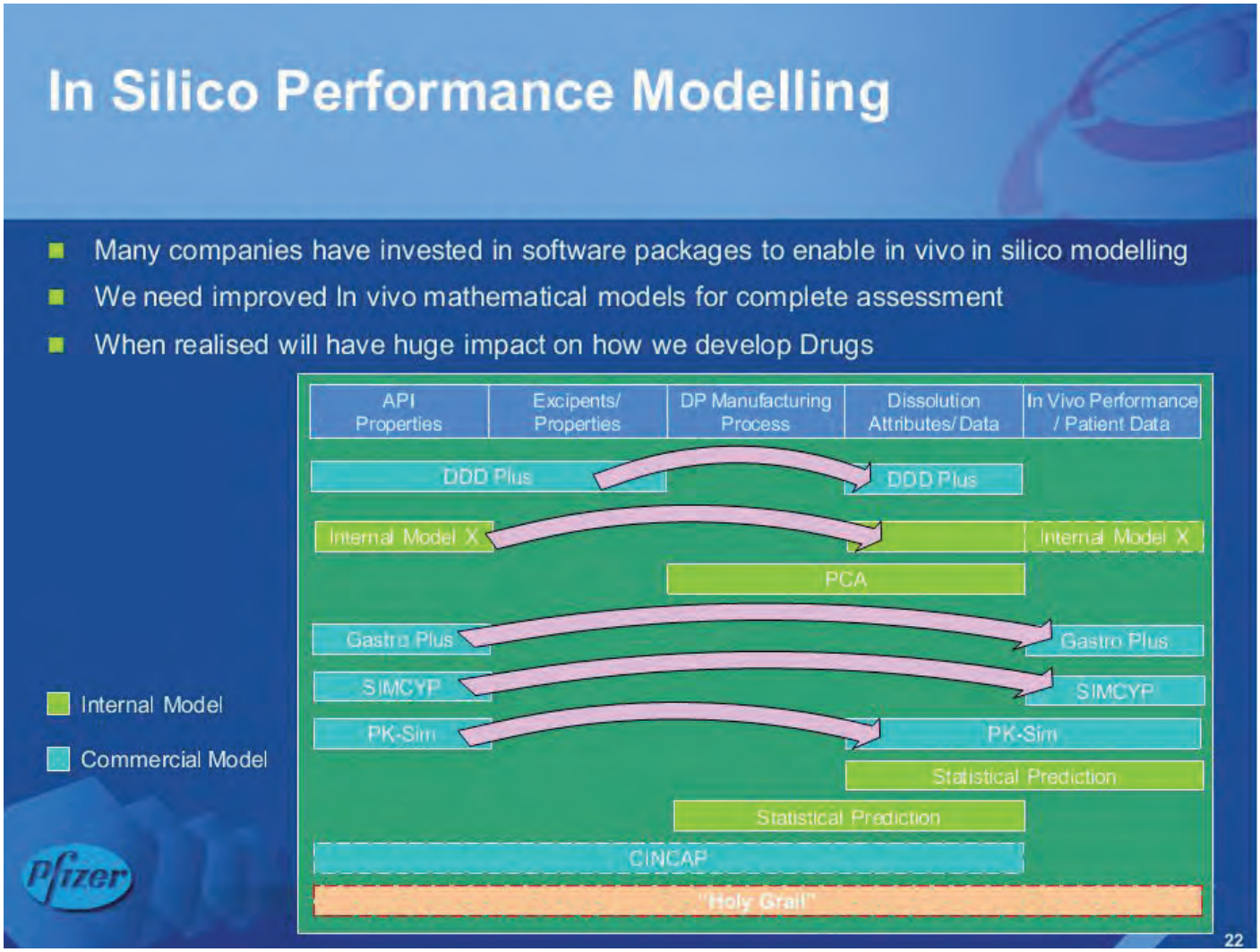



Fig. 18: In-silico performance modeling, slide presentation by Sally Greb, Pfizer Ltd, May 2010, see http://pasg.org.uk/PASG), May_2010_Presentations/ Presentations_Session_3/Sally%20Greb%20QbD%20for%20Dissolution.pdf.

**Research Topic 3: Is Acupuncture related to Bioelectric Medicine?**

Acupuncture is a hot topic and part of alternative medicine. Interestingly, a convergence of alternative medicine and school medicine starts to take place leading to professorships in alternative and complementary medicine at the Universities of Bern and recently at the University of Basel. Due to the system of direct democracy, alternative medicine is covered in Switzerland by health care insurance if the primary physician is sending the patient for acupuncture. In Germany, acupuncture is also accepted as a treatment and being covered by health care insurance.

This is different in other countries despite the fact that the GERAC studies at the Charité Hospital in Berlin showed acupuncture to be an effective pain treatment without side effects: see *https://www.g-ba.de/downloads/40-268-487/2007-09-27-Abschluss-Akupunktur.pdf.* Since the scientific explanation of this treatment is lacking, research topic 3 is mandatory and will lead to new insights in bioelectric medicine. During the Lake Nona Impact Forum 2018, *(https://lakenonaimpactforum.org/*), Peder Olofsson, (Center of Bioelectric Medicine, Feinstein Institute, see *https://www.feinsteininstitute.org/programs-researchers/bioelectronic-medicine*, presented a novel approach based on bioelectric medicine, see research road map *https://www.nature.com/articles/nrd4351*. In this forum the House Speaker Paul Ryan, see *https://en.wikipedia.org/wiki/Paul_Ryan*, proposed acupuncture for pain treatment in lieu of using fentanyl (opioid), see (*https://www.drugabuse.gov/drugs-abuse/opioids/opioid-overdose-crisis*.

The scientific community needs to be open minded to develop unconventional ideas and hypotheses that may be correct or incorrect.

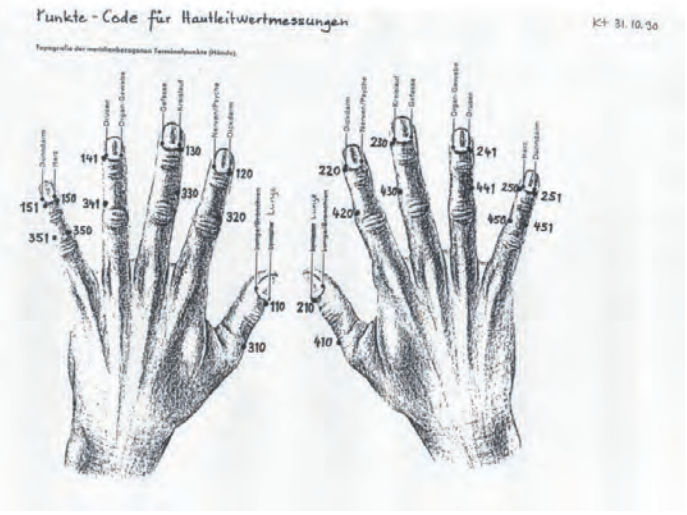



Fig. 19: Acupuncture points (Courtesy of Dr A Comunetti, private communication)

For this reason, the following hypothesis needs to be addressed: Is acupuncture linked to bioelectric medicine on the basis of Axiom 3 (Schrödinger), Axiom 4 (Schrödinger/Prigogine) and Axiom 5 (Fröhlich)? Interestingly, in the 1990's a group of researchers at Roche in Basel started a research project to obtain a better understanding of acupuncture and acupuncture points. For this purpose, Dr Angelo Comunetti, a very talented physicist, was asked by this group to develop and construct a device measuring the skin conductance with a less subjective and less invasive method on the body using an electrode of 2 mm diameter by applying a constant defined force, this is in contrast to most commercially available instruments. He could confirm that at acupuncture points, the skin conductance is a maximum, and is specific for each acupuncture point (fig. 19).

For measuring the skin conductance, Comunetti applied rectangular pulses with a frequency of 20 Hz which included higher harmonics of the alternating current. The observed signal is a rectified current of 5 s duration showing a characteristic decrease, which is affected by repeating the measurements. Thus, the analytical measurement seems to induce changes in the biological system. This result is not surprising in context of axiom 5 (Fröhlich), since in the field of quantum mechanics, this problem is well known, see *https://en.wikipedia.org/wiki/Measurement_problem*.
However, at that time, the result was confusing, leading to the decision of the research group at Roche to stop further research activities in this area (see

*A Comunetti, S Laage, N Schiessl, A Kistler, Characterization of human skin conductance at acupuncture points, Experientia 51 (1995) 4, 328-331).*

This decision makes sense in case it is interpreted on the basis of the classical laws and does not take into account quantum mechanics. This is a very speculative hypothesis, but worth to be seriously studied. In this context, the author is wondering whether the application of bio-impedance spectroscopy using specific frequencies at specific acupuncture points may lead to new therapies.

The confirmation or rejection of Axiom 5 is of fundamental interest: Is the Fröhlich condensation a macroscopic quantum mechanical effect comparable to the effect of superconductivity at higher temperatures in the inorganic world?

Bio-impedance spectroscopy is not part of the mainstream research being based on the physical principle of dielectric spectroscopy, a sub-category of Electric Impedance Spectroscopy, see *https://en.wikipedia.org/wiki/Dielectric_spectroscopy*. Many biosensor systems use this method as a label free technique to measure concentration and to detect dangerous pathogens such as Escherichia Coli and Salmonella, as well as yeast cells. This method is well established in biochemistry. Interestingly, the same high-tech method used for the diagnosis and subsequent treatment of patients is considered as a type of alternative medicine. However, the therapeutic results (personal communication) of therapists who did not want to be mentioned in this article reported were very intriguing.

## Proposal for a major Research Initiative in Humanities

This proposal has a very high societal impact comparable to the Human Genome Project.
In this context, Prigogine and Stengers emphasize that the laws governing processes far from equilibrium in an open system are also valid in the emerging field of computational sociology being part of the humanities, see

*«Order out of Chaos», Man's New Dialogue with Nature, VERSO, ISBN - 13: 978-1-78663-100-8,*

Thus, thanks to computational science, all scientific disciplines start to converge, see
*Hans Leuenberger, (R) Evolution der Pharmatechnologie, Pharma-Journal 1.2015, see http://www.galenusprivatstiftung.at/60.0.html).*

*However, it is important to keep in mind that* ***any model is nothing more than a description, even*** *the textbook of the very successful theory of quantum mechanics (QM) is the result of heuristic rules based on the* ***Copenhagen convention.***

***Thus, the QM textbook is not a holy bible carved in stone*** with the need for interpretation, see *https://en.wikipedia.org/wiki/Copenhagen_interpretation*), ***QM or any other model should not become a new religion. Such an unholy alliance between religion and politics needs to be avoided.***

***For this reason the convergence of all scientific disciplines is a prerequisite and the societal impact of the humanities will become comparable to the current impact of the exact and engineering sciences.***

***The century of Artificial Intelligence computational science will lead to political solutions that can be explained based on a validated truthful scientific foundation.*** However, it is a prerequisite, that the politicians and the specialists involved must take an appropriate oath similar to the ***Memorandum on scientific integrity*** and the ***handling of misconduct*** in the scientific context of the ***Swiss Academies*** (see chapter Prologue).

Since public research initiatives need to be financed using tax money, it is important to show to the tax payers the return on investment, which is often easier in the field of engineering sciences than in the humanities. Research topic and results are based on hypothesis to be accepted or rejected. Thus, it is helpful to study a practical example such as the history of the Pharmacenter at the University of Basel:

Prof Dr Heinrich Ursprung, Secretary of State of the Swiss Federation, had the great vision for an optimal return on investment to concentrate research and education of pharmaceutical scientists at two locations in Switzerland close to the Federal Institutes of Technology (Lausanne and Zurich). His plan was realized in the western part of Switzerland at the University of Geneva that resulted in a success story. What if this idea would have been realized in Lausanne? Prof Gian-Reto Plattner convinced the Federal Institute of Technology Zurich (ETHZ) to establish research laboratories of systems biology at the University of Basel close to Novartis and Roche, which for Basel is also a success story. What if the research and education of pharmacists would be concentrated in Basel, too? What if the Center of Excellence in Pharmaceutical Sciences (CEPS) would have been continued? Thus, the pharmacy professors at the University of Basel and at the Federal Institute of Technology would share their lectures by video with the students in Basel and Zurich stimulating research and innovation at both sites. What if the vision of Prof Gian-Reto Plattner would have been realized to establish a close link between the Pharmaceutical Department of the University of Basel and the School of Life Sciences of the University of Applied Sciences, offering common curriculum for Pharmaceutical PhDs and Pharmaceutical Engineers? What if the proposals published in 2*001, see NZZ July, 24, p.12,* would have been implemented? What are the ***democratic means to avoid unpopular top-down decisions*** to reach this goal? Can the proposed Research Initiative in Humanities further develop the Swiss System of Direct Democracy (SSDD), facilitating to find the best solution? What are the prerequisites in case of complex issues?
Due to the high social impact of this research initiative, it is recommended to include in this study the history of Switzerland and

Europe ( see Epilogue). In this context it is important to notice that Switzerland was involved in the European revolutions of the 19th century:
*Eric Hobsbown, The Age of Revolution 1789-1848 FIRST VINTAGE BOOKS EDITION, AUGUST 1996, Originally published in Great Britain in hardcover by Weidenfeld & Nicolson, London, in 1962. ISBN- 0-679-77253-7).*

## Epilogue

Artificial Intelligence is the emerging megatrend of science and technology being linked to computational science and the digital revolution. Since Switzerland cannot live in an isolated gated, museum like community without relations to its neighbors, the impact of the six axioms in the socio-economic field is a scale invariant topic leading to the following questions regarding the future of Switzerland and Europe:

What were the reasons, Switzerland was the only country in Europe introducing its Federal Constitution of 1848, a tailor made version of the American Constitution of 1787? The liberal revolution in Switzerland started in the Canton of Basel in 1830 since the people in the rural part of the Canton suffered from the aristocratic regime of the city of Basel and lead to the separation of the Basel Canton in two parts. Interestingly, 200 years later the people involved still do not trust being ruled by a common government. Thus, it is not surprising that in 1830 the people of the Canton of Basel still remembered the events that happened during the peasant war in 1653, see
*Hans Leuenberger, Niklaus Leuenberger, der angeblich reuige Revolutionär, Jahrbuch Familienforschung Schweiz 2015 / Vol. 42, (2015) 159-177,* see *www.ifiip.ch/download*, articles.
The history of the peasant war is a dark chapter of Switzerland, see *http://www.hls-dhs-dss.ch/textes/d/D8909.php*. The following «What if?» questions arise:
What if the Bernese government would not have violated the Murifeld peace-treaty of 1653 that was signed by representatives of the government and the rebels? What if the Bernese government would have honored the Federal Charter of Huttwil of 1653, which included in the first paragraph, that there is no difference between catholics and protestants, a first attempt to introduce the freedom of religion? Thus, the Federal Charter of 1653 could be adopted by Switzerland as an updated version of the Federal Charter of 1291.
In 2048, Switzerland will celebrate 200 years of its most successful Federal Constitution. The success of Switzerland is based on the Federal Constitution of 1848, which lead to the introduction of a common currency, abolish customs between the cantons, granting a high autonomy of the states (cantons), to enjoy their individual culture, language, religion, mindset and education, allowing four different idioms (German, French, Italian and Romanesque) as officially recognized languages. Compared to other countries, Switzerland assures that professors at the Universities, teachers at the colleges and schools receive adequat salaries that the students are well educated, a high percentage speak English, the official internal language of Novartis and Roche with headquarters in Basel. After 1848 Switzerland's economy started to boom and major pharmaceutical, food, high-tech watch and precision machinery companies were founded, railways were built and the country became a clean and beautiful tourist destination offering excellent Swiss cheese, chocolate, precious watches, excellent healthcare facilities and hosting a booming pharmaceutical industry.
Last but not least, the following «What if» question? needs to be discussed: What if in the 19th century other European countries would have adopted the Swiss Constitution of 1848 which is more or less a copy of the American Constitution of 1787? What if the European Union would have adopted a tailor made Swiss Federal Constitution? Would such a European Federal Constitution lead to the same sustainable, peaceful and economically prosperous solution as in small and beautiful Switzerland? Was Winston Churchill impressed by the Federal Constitution of Switzerland that he chose Switzerland to give his presentation regarding a United Europe at the end of the second world war?, see *https://www.youtube.com/watch?v=DWjrhCewhCg*.

## Acknowledgements

The author thanks all his numerous friends who supported him and apologizes that there is not enough space for mentioning all the names and titles. He is happy to still meet friends he knew at the company Sandoz (today Novartis), namely Helmut Eckert, Jürg Meier, Ruedi Wäger and Stefan Winzap. The latter was assisting him to establish the student training laboratories at the University of Basel. The author acknowledges the support of Heinz Sucker and Stephan H Guttmann at Sandoz and thanks especially Georgios Imanidis, his deputy as chairman at the Institute of Pharmaceutical Technology (IPT) and Claudia Reinke, who also assisted him at the Swiss Academy of Engineering Sciences SATW to introduce the concept of SATW Technical Weeks at Swiss Cantonal schools. Both collaborators played a crucial role in the planning of the Pharmacenter. The author is very grateful to his friends at SATW, namely Werner Richarz, Branco Weiss, Martin Lendi and the SATW presidents, he served, namely Ambros Speiser, Jean-Claude Badoux and Willi Roos, who awarded him to become the youngest Honorary Member of SATW in 2001. The author is thankful being invited to the annual dinner of former SATW presidents with the participation of Prof Heinrich Ursprung in a relaxing atmosphere of forgiveness which is especially acknowledged. The author thanks his friends of the Swiss Society of Pharmaceutical Sciences SGPhW, who allowed him to honor personalities who deserved the Reichstein medal, designed by Willy Engel, Thun. Ruedi Brenneisen is acknowledged for organizing the SWISS PHARMA SCIENCE DAY.
Last but not least the author thanks Cornelia D Sonntag of the Galenus Privatstiftung in Wien, see *http://www.galenusprivatstiftung.at/16.0.html*, James Hickman of the University of Central Florida for fruitful discussions and is thanking especially Hartmut Derendorf, chairing the College of Pharmacy (COP) at the University of Florida for being invited in 2018 as Member of the Adjunct Faculty, and Thomas Schmittgen, current chairman, to give lectures in Pharmaceutical Technology, Larry Lesko (formerly at FDA and COP), and Stephan Schmidt, associate director of the Lake Nona Campus.

***Contact***

Hans Leuenberger, PhD
Professor emeritus Pharmaceutical Technology
University of Basel
Adjunct Professor
University of Florida, College of Pharmacy,
Lake Nona Campus.
*hans.leuenberger@ufl.edu;*

IFIIP, Institute For Innovation in Industrial Pharmacy
«Hans Leuenberger PhD – IFIIP»
P.O. Box 568891
Orlando, FL 32856-8891
*hans.leuenberger@ifiip.ch*