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Right First Time
Computer-Aided Scale-up

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Right First Time: Computer-Aided Scale-up

for manufacturing solid dosage forms with a shorter time to market

Hans Leuenberger[1,2,3]*, Michael N. Leuenberger[2] and Maxim Puchkov[3]

Summary

"Right First Time" is today the actual slogan of all major pharmaceutical companies. However, a closer look to the generally accepted workflow during pharmaceutical R&D, scale-up, product launch, etc. of a solid dosage form, reveals, that the situation is not at all ideal. In fact, the first clinical trials of a new active substance start in general with a "service" dosage form – often a capsule formulation –, which is not identical with the "prototype" formulation in a later clinical phase, when the marketed dosage form is realized. Such a preliminary "service" dosage form cannot comply with the idea of "Right First Time". The subsequent follow-up activities, the fast prototyping, the bioequivalence testing, the scale-up procedures add additional uncertainties, which slow down the process of time to market and yield finally a 2–3 sigma manufacturing performance. If there is a goal for a final six-sigma quality of the marketed dosage form, it is mandatory to start the clinical phase I with the desired final marketed dosage form. Thus, no service form and subsequent bioequivalence testing is needed. Long-term stability testing, with the right formulation can be started at the time of the first clinical trial. This ambitious goal is achieved by applying virtual R&D reality, which includes the replacement of lab work by computer, increasing the productivity, and a computer-aided scale-up approach. In this context, it will be a prerequisite to abandon the 80%/20% Pareto rule and to implement thanks to e-R&D and e-Manufacturing a 100%/10% concept, i.e. to achieve a "Zero Defect" Manufacturing Performance using much less resources. Like in the aircraft industry, substantial savings should be possible. The paper discusses solutions to facilitate the scale-up process using the following tools: 1) F-CAD (Formulation – Computer-Aided Design) in order to check the robustness of a specific formulation, 2) A specific computer-aided scale-up model, which takes care of the most critical unit operation, i.e. the wet agglomeration process, 3) Virtual large-scale equipment simulators.

Keywords
Right First Time, Scale-up issues, Dosage form design and optimization, in silico design and experiments, Operational Excellence, Process Analytical Technology (PAT), Quality by Design (QbD), faster time to market, e-Research and e-Development (e-R&D), e-Manufacturing, process and formulation understanding.

1. Introduction:

1.1. First contact with the reality

Drug-excipient compatibility studies:
The corresponding author joined Sandoz Pharma Ltd. in 1971 (see: http://www.ifiip.ch/content/de/about-ifiip/cv-head.html) as head of the "drug-excipient compatibility" laboratory of the Pharmaceutical Analytical R&D Department. Before he joined 2 years later the Pharmaceutical R&D Department, the drug-excipient compatibility tests were performed as follows: An accelerated stability test was done at 50°C and compared to 4°C with drug-excipient powder mixtures, consisting of the drug and functional excipients, simulating formulations according to a factorial design [1] (see: www.ifiip.ch/content/de/downloads/articles-download.html, A Factorial Design for Compatibility Studies in Preformulation Work). The degradation of the drug substance was determined using a semi-automated TLC (Thin Layer Chromatography). For a facilitated detection of the drug and its degradation products, the drug has been labelled by Tritium. Today, no labelling is necessary and such tests are performed much faster with the automated equipment of RPD Tool (http://www.rpdtool.com/), using HPLC, respectively UPLC for chemical analysis (see Fig. 1). Fig. 1 shows a diagrammatic representation of the automated equipment. The task needs just a fraction of time and laboratory work, compared to the past. Thus, savings of the order of 60%–80% are possible. In addition, this equipment is able to measure, if desired, physico-chemical properties of the formulation and of its components (see presentation "Automated stability assessment – An approach for rapid formulation development" in http://www.ifiip.ch/content/de/downloads/download-presentations.html).

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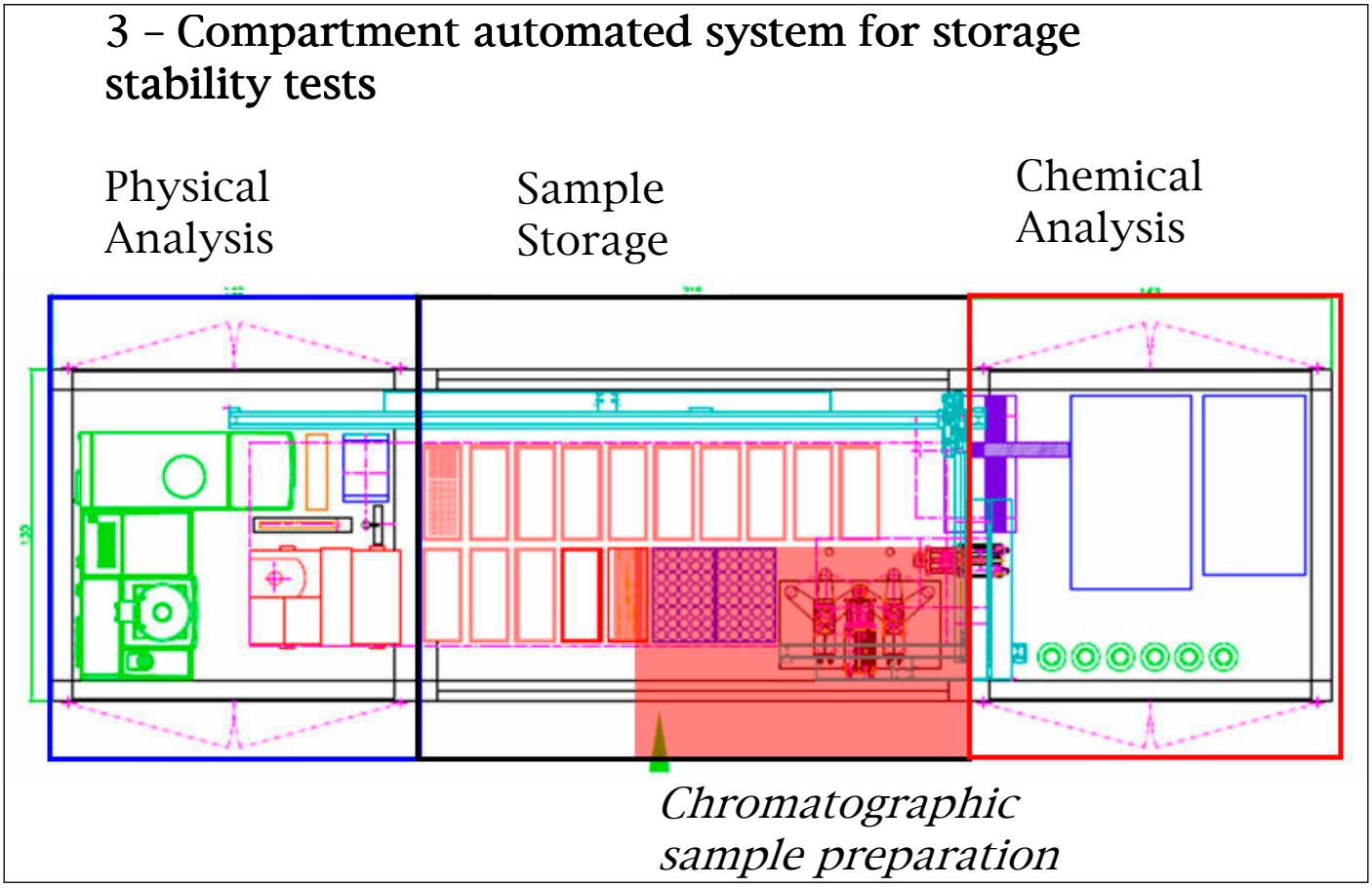


Fig. 1: System for testing drug-excipient compatibility and storage stability of prototype formulation or final marketed dosage form. (RPD Tool, 4123 Birsfelden, Switzerland).

On the one hand, the pharmacopeia does not specify which properties of the drugs, excipients, formulations need to be determined in a mandatory way. On the other hand, some very relevant properties of the starting material, resp. formulation are not included in the pharmacopeia.

Innovations in a highly regulated environment:
It became evident that innovative projects have difficulties to be implemented (see: http://www.ifiip.ch/content/de/innovations.html). Questions such as "Corresponds this new equipment to the cGMP rules?" or "Is this new process already accepted by FDA?" do not boost necessary improvements concerning process technology etc. In addition, the IP (Intellectual Property) department of the pharmaceutical company will tell to the scientist in the R&D Department that the new idea is not worth to be protected due to the fact that a pharmaceutical company is not at the same time an equipment manufacturer. Unfortunately, equipment manufacturers do not have in general enough resources and/or are lacking of a pharmaceutical experience.

The wet agglomeration process:
The topic "agglomeration" is of interest to many different industries [2] (see: http://www.ifiip.ch/content/de/downloads/swiss-pharma.html SWISS PHARMA Issue 7–8, 1985). In the pharmaceutical industry, the most critical step is the addition of the correct amount of granulating liquid during the moist agglomeration process. Thanks to Marcel Dürrenberger (Sandoz Engineering Department), and Dr. Jürgen Werani (Sandoz Pharmaceutical Manufacturing Department) it was possible, at that time, to develop in-house the first power consumption "PAT" device, which monitors the wet agglomeration process, *and* controls the amount of granulating liquid [3], see: "Granulation, New Techniques", in http://www.ifiip.ch/content/de/downloads/articles-download.html, respectively [4] "Scale –up of Granulation Process with Reference to Process Monitoring". This very early power consumption PAT (Process Analytical Technology) device reduced the statistical variance of batch-to-batch quality of the yield of the granule size distribution between 90 µm and 710 µm by more than one order of magnitude:
Table 1 (see below): Yield of the granule size distribution as a result of a PAT controlled addition (Automatic mode) of the granulating liquid compared to the classical addition using a constant amount of granulating liquid, see M. Dürrenberger, J. Werani, cited in [2] http://www.ifiip.ch/content/de/downloads/swiss-pharma.html Issue 7-8, 1985.

Type of mode	yield (% w/w) 90–710 µm	% undersize < 710 µm	undersize < 90 µm
Manual mode n = 20 batches	81.03 ± 2.42	88.30 ± 2.05	6.80 ± 0.51
Automatic mode n = 18 batches	91.45 ± 0.36	96.80 ± 0.31	5.40 ± 0.35

Table 1 describes the yield of the granule size distribution as a result of a PAT controlled addition of the granulating liquid. The regime of "Automatic Mode" is based on the power consumption profile of the formulation and the equipment used, taking into account the particle size distribution and the moisture content of the starting material [3], see http://www.ifiip.ch/content/de/downloads/articles-download.html Granulation, New Techniques. Thanks to the much better batch-to-batch quality, the control settings of the high-speed tableting machine could be kept constant and did not need any batch specific adjustments. These excellent results convinced the management to introduce at all relevant production sites in the Sandoz world identical high-shear granulators, equipped with such a power consumption control device. This has been an

extremely wise decision at a very early time in the spirit of today's PAT and QbD (Quality by Design) Initiative.

Surface response research / formulation sensitivity analysis:
Early publications at Sandoz include the application of mathematical modelling [5, 6], see http://www.ifiip.ch/content/de/downloads/articles-download.html. Drug Delivery Systems for Patient Compliance. The paper shows the landscape of a placebo formulation taking into an account the quantitative effect of excipients and of process variables, exploring the design space. In today's spirit of QbD such an approach corresponds to a sensitivity analysis concerning the robustness of a formulation. Unfortunately, such a study in the laboratory needs too many resources, which makes such an approach – based on an extensive laboratory work – unrealistic.

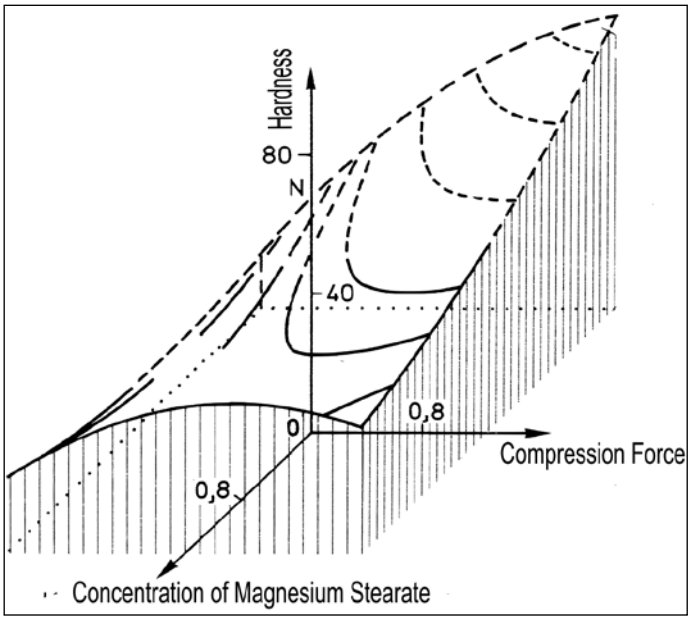


Fig. 2: Sensitivity analysis: Landscape representation of a tablet hardness as a function of the compression force and the concentration of magnesium-stearate in a formulation [5,6].

The high batch-to-batch variability of product properties of many pharmaceutical unit operations have prompted the PAT and QbD initiative of FDA.

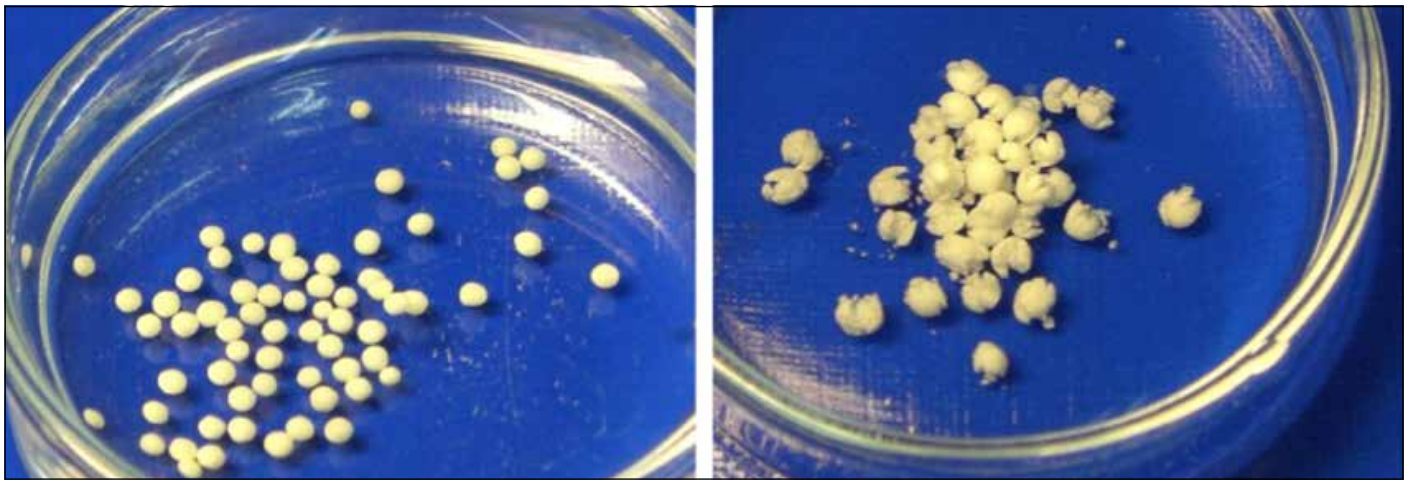
1.2. Process Analytical Technology (PAT) and Quality by Design (QbD) Initiatives

FDA became alerted due to the fact that the number of innovative medical products to be registered is decreasing, and that, at the same time, the development costs are constantly rising. In addition, the manufactured products often need a final quality screening, i.e. to sort out defectives. It has been reported that the manufacturing performance of the pharmaceutical industry complies with ca. 2-3 sigma, which is low compared to the chip industry with its six-sigma-performance. Six-sigma means, practically, to have a production with zero defectives. In order to achieve such a performance, it is necessary to check and optimize each pharmaceutical unit operation, and each formulation. A typical and critical unit operation concerning scale-up is the wet agglomeration process [3,4]. Mid February 2004, Helen N. Winkle, Director of FDA's Office of Pharmaceutical Science (OPS) together with Dr. Ajaz Hussain, at that time, Deputy Director of OPS paid a visit to the University of Basel. The central theme was the PAT research work of the Institute of Pharmaceutical Technology, which received in 1994 the Innovation Award of the Governments of Basel-City and Basel-Country for the special concept of a quasi-continuous granulation line developed together with the equipment manufacturer Glatt AG in CH-4133 Pratteln, Switzerland. The visitors from FDA had the opportunity to see this technical solution at the Goedecke/Pfizer solid dosage form plant in Freiburg, Germany. This granulation line combines the advantages of a batch and a fully continuous process, i.e. it is possible to produce just a batch of the size of 6 kg or a multiple of n of 6 kg with n up to n = 100, i.e. 600 kg. It is important to realize that the small-scale batch and the large-scale batches are manufactured with the same equipment! This innovation takes care of the concept of "Right First Time": The first 6 kg are fine and have the same quality as the consecutive ones! In contrast to a real continuous process, there is no need to wait until the process has reached its equilibrium. Dr. Jürgen Werani, at that time Area Leader Europe RFT (Right First Time) at Pfizer Global Manufacturing, has been very much in favour of such a concept [7] (see: http://www.ifiip.ch/content/de/downloads/download-presentations.html "Continuous processes in manufacturing solid dosage forms").

This concept goes beyond the earlier idea of Sandoz Pharma Ltd. (see chapter 1.1) to install at all their manufacturing sites the same equipment in order to have the same quality everywhere. The innovation, in case of the semi-automated granulation line, is the following: both, i.e. the development and manufacturing sites use the same equipment! Thus, it is possible to develop and optimize the first formulation "right first time" and to manufacture small-size and large-size batches with the same equipment and with the same quality. The scale-up job, using a semi-continuous equipment, will be different from a classical one, as the scale-up exercise will be executed in the 4th dimension [8]. If the formulation is robust from the very beginning, i.e. "right first time", no problems should be expected.

1.3. State-of-the-art

The PAT and QbD initiative has been well received by the manufacturing departments of the pharmaceutical companies, applying sophisticated and expensive "at-line, in-line, and on-line" measurement devices to get a better formulation and process understanding during pilot plant manufacturing. In the pre-formulation and early development departments the situation is more complicated due to the fact that there are many projects in the pipeline with more or less equal priority. The problem is the presence of the high project attrition rate [9]. For this reason it is understandable that the pharmaceutical industry follows the 80%/20% *Pareto rule,* i.e. to invest 20% of the resources to obtain 80% of the goal. The disadvantage of such an approach is that only a manufacturing performance of ca. 2-3 sigma can be obtained [9] (see: www.ifiip.ch/content/de/downloads/swiss-pharma.html, Issue 7-8, Year 2009, www.ifiip.ch/content/de/downloads/download-presentations.html "QbD Initiative Impact on Development and Manufacturing". According to the *Pareto Rule* the first dosage form, often called "service form" for the early clinical trials, is a relatively simple one, e.g. a hard-gelatine capsule formulation. Then, the final dosage form for the market is designed in clinical phases II, IIb or early phase III depending on the company's specific nomenclature. It is probably the result of services of major consulting companies that the global pharmaceutical industry has adopted practically the same approach in order to streamline the workflow and to reduce overhead costs. A typical "service dosage form" consists of the necessary amount of drug and standard excipients such as lactose, cornstarch etc. The question arises if such a standard procedure is the best one? Why not a standard capsule or tablet formulation consisting of a mixture of the drug substance with e.g. the new microcrystalline cellulose MCC Sanaq Burst, see: http://www.pharmatrans-sanaq.com/prod.html. This new cellulose is the diamond among the different crystalline cellulose modifications: MCC Sanaq Burst is a multifunctional excipient with superdisintegrant, binder and filler properties, which can be used as direct compression vehicle. Due to the better taste than the other types of cellulose, MCC Sanaq Burst has a great potential to become the vehicle of choice for oral dispersible tablet (ODT) formulations (see video of the disintegration of a prototype MCC Sanaq Burst ODT formulation compared to an ordinary MCC formulation at http://www.ifiip.ch/content/de/downloads/multimedia.html). This new type of cellulose was studied at the University of Iowa by Prof.



Fig, 3: Disintegration of classical MCC pellets (Avicel PH 102) and MCC Sanaq Burst pellets with a drug load of 80% (w/w) Chloramphenicol after staying 5 sec in water (study sponsored by Pharmatrans Sanaq [10]).

V. Kumar and during several PhD studies (V. Bolzano, E. Darronqui, M. Lanz, F.S. Müller, and M. Rumman) at the University of Basel. A recent study [10] at the University of Duesseldorf revealed that MCC Sanaq Burst could be used for manufacturing fast disintegrating pellets by the extrusion method (see Fig. 3).

The standardized procedure of manufacturing service forms has a dangerous lack of flexibility, as all "service dosage forms" are treated in the same way, independently of the drug indication.

Unfortunately, the current first "service" dosage form is by nature not an optimized and robust one. The regulatory guidelines do not allow major changes in the formulation during the clinical trials, i.e. the initial formulation has been "frozen". Taking into an account all factors systems research tells us in a straightforward way that it is practically impossible with such a concept to achieve a six-sigma quality performance. The reason is the following: Errors are propagating and it is extremely seldom that errors cancel each other. Fig. 4 illustrates this situation with the following flow chart:

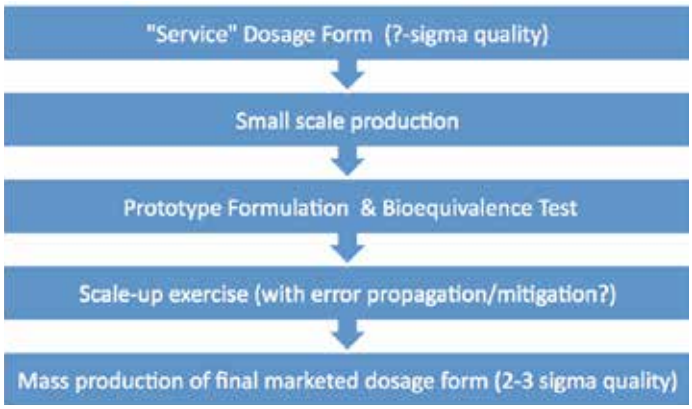


Fig. 4: Flow chart "From small scale production for first clinical trials to large scale production". This flow-chart covers the "Industrialization" part of FDA's Critical Path Initiative.

FDA considers the "Industrialization process" as a critical path (see: FDA Whitepaper March 2004, Three Dimensions of the Critical Path in "(Invited) Presentation, Visit at FDA 2005" at http://www.ifiip.ch/content/de/downloads/download-presentations.html. One of the critical steps is the "Scale-up exercise", where small- and large-scale equipment is involved. The following discussion excludes the problem of possible human errors, which can always happen. The variety of different sizes of the relevant process equipment in the pharmaceutical industry is impressive. Probably, on a global scale, the equipment is as different in size and type as the vehicles of the Taxi-Service Enterprise at the respective geographical location, i.e. ranging from a low-cost motorcycle with a sidecar, to an expensive "stretch-limousine" with all necessary and unnecessary accessories. Why do we make such a comparison? What do small and large-size vehicles and small and large-size pharmaceutical equipment, such as a mixer/granulator, have in common? Both the vehicles and the mixer/granulators do their job. However, none of them complies with Buckingham's Theorem of geometrical, kinetic and dynamic similarity, see [4] article, resp. http://www.ifiip.ch/content/de/downloads/articles-download.html Scale-up of Granulation Processes with reference to Process Monitoring. In other words, there is no self-similarity between the small- and large-scale equipment concerning shape and functionality.

Indeed, the performance of the vehicles is very different, i.e. a small-scale car with an economic motor cannot be compared with a high-speed "Formula 1" racing car. The differences in their performance can be quantified by power consumption of the motor or simply by the noise developed etc. This can be also done, as an example, in case of a mixer/granulator, see the slide show of gsk (Glaxo Smith Kline) at http://www.fda.gov/ohrms/dockets/ac/02/slides/3841s1_05_Rudd/sld016.htm

The acoustic signals of the mixer/granulator in this gsk-slide show represent a "fingerprint" of the formulation *and* of the equipment used. This "fingerprint" can be very helpful for keeping the same batch-to-batch quality performance.

The power consumption of a car depends on its weight and its load, as well as on the landscape where the car is driving, being different in a flat or mountainous area. In case of a mixer/granulator the power consumption profile depends on the size of the equipment and on its load (batch size) *and* on the formulation. The formulation has the property of the "landscape" in Fig. 2.

The goal of the wet agglomeration, and the subsequent drying process, is to obtain the necessary granule size distribution which favours granule flowability and compressibility for subsequent tableting. As the density of the granules plays a role, it is advisable, to measure the power consumption profile (PCP) during the wet agglomeration process.

In order to analyse and understand PCPs of the same formulation using equipments of different size, it is necessary to deduct the no-load power consumption to get a common base-line. The resulting profile describes the behaviour of the formulation during the wet agglomeration process, which is specific for the formulation *and* the equipment (see [2] resp. http://www.ifiip.ch/content/de/downloads/swiss-pharma.html, SWISS PHARMA, Issue 7-8, 1985 resp. [3,4]. resp. http://www.ifiip.ch/content/de/downloads/articles-download.html "Granulation, new techniques, "Scale-up of granulation processes with reference in process monitoring". Interestingly, it became evident that the native so-called "green granules" show a self-similar granule size distribution, if normalized with its mean value, as a func-

tion of the granulation liquid added [2]. This may be of interest for validating in-situ measurements of the evolving granule size distribution during the wet agglomeration process.

2. The New Approach

2.1. Right First Time

The new approach consists in replacing expensive laboratory work by computer deskwork, i.e. *in-silico* design. This is possible, thanks to the availability of relatively cheap *high-performance computer hardware* and special software such as F-CAD based on a first principle approach using *mass-parallel computing* and *cellular automata,* [9], see http://www.ifiip.ch/content/de/downloads/articles-download.html SWISS PHARMA, Issue 7-8/09. This article with the title "Implementing Virtual R&D Reality in industry: *in-silico* design and testing of solid dosage forms" describes how laboratory work can be replaced by *in-silico* work. This new approach is however not at all a job-killer, it is just a new and effective tool! It is the expert in pharmaceutical technology and her/his ideas which will be more and more needed to do an excellent job. It is not the tool, i.e. the knife, it is the artist who creates a beautiful sculpture and it is the expert using the tool to design an optimal formulation. In addition, the laboratory work will become much more exiting, e.g. by *validating with a very few experiments* the formulations, suggested by F-CAD! And it will be an additional motivation to get the result *right first time!*

Thus, already at an early stage of the development with many interesting drug candidates, and with a small amount of drug substance robust formulations can be manufactured, i.e. the productivity of the development laboratory will significantly increase. According to the proof of concept [9] the desired dosage form can be manufactured *"right first time".* Most important, it is possible to create *in-silico,* i.e. without additional laboratory work, a landscape similar to the one in Fig. 2. However, the focus in this "Landscape", i.e. "Sensitivity Analysis" is not the tablet hardness, but the *drug dissolution profile* of the formulation studied. Interestingly, on the one hand, the drug dissolution property is extremely sensitive to changes in the formulation. On the other hand, it is very difficult to model this property, as ANN-studies have shown in [11] see http://www.ifiip.ch/content/de/downloads/download-presentations.html "Pharmaceutical process optimization with Artificial Neural Networks".

F-CAD has the advantage to be based on cellular automata, i.e. on a first principle approach [9].

The beauty of this "first principle approach" is the fact that the main contribution of the " drug dissolution profile" is related to the composition of the formulation and to the intrinsic dissolution rate of the drug substance in different buffer solutions. The difference in the type of equipment (basket-, resp. paddle-apparatus) is taken into account by means of a "fine-tuning" calibration.

Knowing the "landscape" of a new drug formulation it is possible to choose *right first time* the desired robust formulation. Within a rigorous concept it would be best to start the clinical trials directly with the final marketed dosage form in order to avoid any later bioequivalence testing (see Fig. 6):

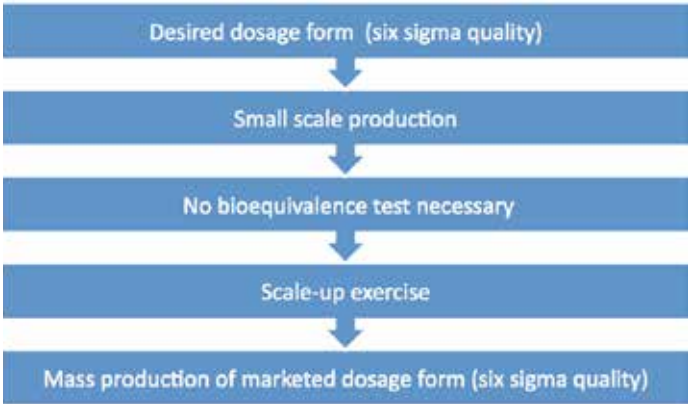


Fig. 6: Flow chart "From small scale production for the first clinical trials to large-scale production according to the new approach starting and keeping a six sigma quality".

The desired dosage form can be the final marketed dosage form, or an advanced type of "service dosage form", which avoids the problem of an adverse drug load effect described in the PhD thesis of Johannes von Orelli [12]. The innovation cycle for such a new "service dosage form" needs not to be the same as in case of an "i-phone", but should show a real improvement: Such an "i-service dosage form", as an example, could consist of fast disintegrating pellets with a drug load of up to 80% (w/w) [10]. Thus for the dosage range finding in the clinical phase I, it will be just the number of pellets being identically, which will define the dose (see Fig. 3).

2.2. Applications of F-CAD

Fig. 7 shows a screenshot of an oblong solid dosage form, which interacts *in-silico* with the aqueous dissolution medium containing a swelling excipient. The picture is a real-time copy of the contents in the computer memory of a high-performance mass parallel computer unit.

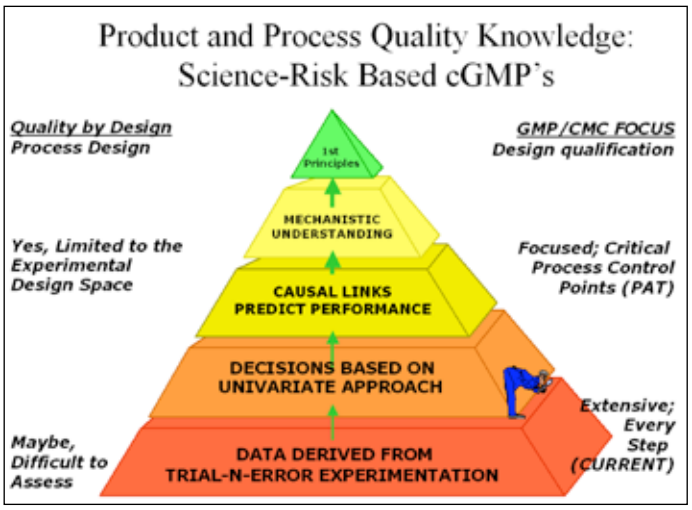


Fig. 5: Knowledge Pyramid (Courtesy FDA, Dr. A. Hussain, FDA).

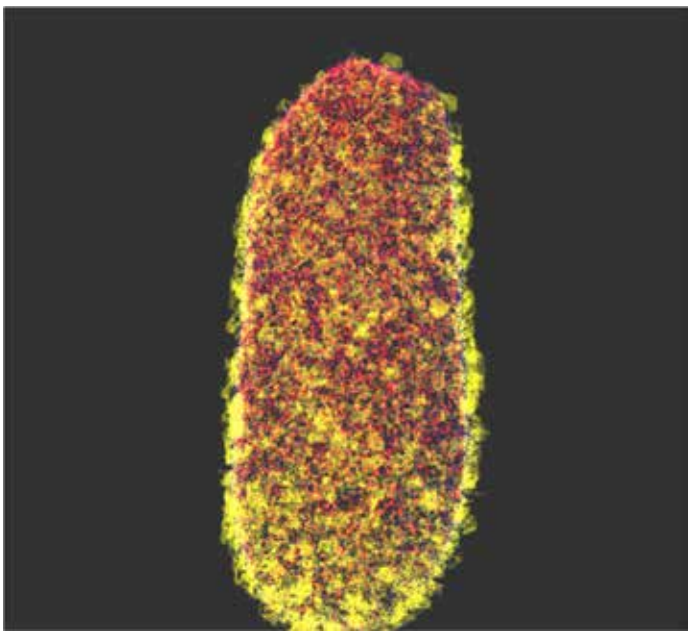


Fig. 7: Screenshot of a computer-generated matrix type formulation, which contains a swelling excipient (yellow) after time t* = 100 sec.

It is evident that it is possible to create with a series of such pictures a fast or a slow-motion movie. The identical experiment in a laboratory would be very time consuming.

The following list of F-CAD applications may not be comprehensive, but summarizes the actual status:

2.2.1. F-CAD [13] can establish in a very short time a "landscape" (see Fig. 2) i.e. "sensitivity" analysis of any drug formulation with the *focus on the drug dissolution profile.* Thus, it is possible with a very low amount of drug substance to manufacture a robust optimal dosage form for the market. Such an approach will speed up the time to market and increase the productivity of a pharmaceutical company.

2.2.2. F-CAD is able to boost the development of innovative dosage forms, if the physicochemical and biopharmaceutical properties of the drug [9] are known, such as for a fast and/or slow drug delivery, including ODT (Oral Dispersible Tablet) formulations or fast disintegrating MCC Sanaq Burst pellets (see: http://www.pharmatrans-sanaq.com/prod.html).

2.2.3. F-CAD can be used for developing combination drugs [14] based on existing (blockbuster or other excellent) drugs to improve patient compliance by reducing the number of dosage forms to be administered, especially in case of elderly patients, suffering from many diseases. Drug – excipient compatibility and stability studies can be done fast by RPD Tool (see: http://www.rpdtool.com/). Combination drugs are of interest to originator and generic drug companies.

2.2.4. F-CAD can be used to facilitate significantly the work of a generic company: F-CAD needs as input only the dissolution profile (in different buffer solutions) of the originator's dosage form and its qualitative composition. F-CAD, then takes care, suggesting a robust formulation with the same excipients.

2.2.5. F-CAD is a powerful tool to explore the robustness of existing formulations: the knowledge of the dissolution rate profile, the qualitative and/or quantitative composition is sufficient. Thus the company involved and or the governmental registration authority will know immediately the quality and robustness of the formulation, or its weakness.

2.2.6. F-CAD is able to speed-up the development of generic drug products which will allow lower cost generics, being in the interest of governments in order to reduce public health care costs.

2.2.7. F-CAD can be of special interest to virtual pharmaceutical companies, outsourcing all services and activities.

2.2.8. F-CAD can be of special interest to companies, managing, buying, selling and licensing IP (Intellectual Property) rights for pharmaceutical companies.

2.3. Hurdles of the drug substance and the role of dosage form design

Typical hurdles for the drug substance are in general its solubility, stability, permeability and the first pass effect (see Fig. 8). The beauty of a drug substance is its intrinsic value, i.e. its pharmacological effect and not the solubility or other external properties. Unfortunately, a cosmetic surgery of the drug substance, in order to improve its solubility, often jeopardizes its therapeutic effect. Thus, it is the role of the dosage form designer to find a tailor-made solution.

Interestingly, each drug substance looks really different, i.e. a tailor made solution is necessary. F-CAD can be very helpful to design an optimal "dress" in order to cover up the deficiencies of the drug substance such as solubility, stability, permeability, short biological half-life etc.

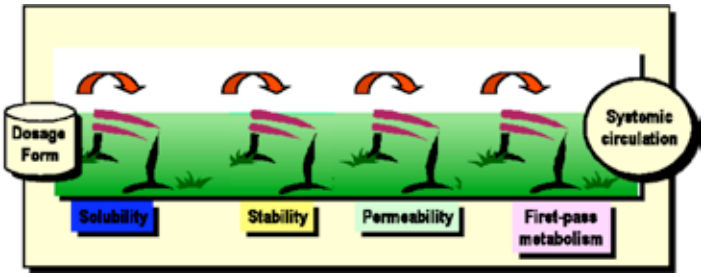


Fig. 8: Some major hurdles for a new drug substance (Courtesy FDA, Dr. A. Hussain, FDA).

Assuming that a beautiful formulation has been developed, what about the problem of scale-up? Unfortunately, this question is difficult to answer in a straightforward way since the hurdles are often not well known. The reason is the following: First, it is essential to know more about the robustness of the *model-formulation,* i.e. the formulation should not be only beautiful but also robust. Such information can be obtained with a "landscape" or "sensitivity analysis" in the design space, which is favoured by ICH 8 [15]. Such an approach is however only feasible if the number of necessary experiments in the laboratory can be reduced.

Secondly, it is important to distinguish the effective influence of the formulation from the influence of the equipment involved during a scale-up exercise. This is illustrated as follows: What is the cause when driving a car in a mountainous area and a wheel breaks down? In the picture of chapter 1.3: Is it the landscape (formulation) or a problem of a car (pharmaceutical equipment) or is the driver, i.e. a human error, the cause? Human error can be to a certain degree eliminated by an intensive training of the driver (see chapter 2.5). It is extremely difficult to make a clear distinction. An attempt is described in the next chapter, which is concerned with one of the most critical unit operations in the scale-up exercise, the wet agglomeration process.

2.4. The wet agglomeration process

The wet agglomeration process has been partly already discussed (see chapter 1.1. and 1.3). The following points are essential:

A) One of the most critical questions is the necessary amount of granulating liquid needed in case of a small and of a large scale equipment,

B) The contribution of the size and type of the mixer/granulator,

C) The influence of the formulation, i.e. more precisely, the influence of the composition with different properties (solubility, swellability, wettability of the excipients and the drug) if water is used as a granulating liquid. The latter point becomes very important if the task of a "landscape" or "sensitivity analysis" is taken from a rigorous scientific point of view: In the search for the optimal formulation, the composition will vary having more or less excipients, which may swell and pick up water, which then cannot form (binding) liquid bridges in the wet agglomeration process. In this context, it is mandatory that the amount of water as granulating liquid is adjusted to the change in the formulation. It is possible to take care of this problem by measuring the complete power consumption profile. Such an approach allows the definition of a specific, normalized quantity π (see Fig. 9) of granulating liquid [2] independent of its composition [16].

The quantity S_5 in Fig. 9 corresponds to the fully developed "capillary state" of the complete powder mass forming one large "snowball" pellet. This "snow-ball like" pellet disintegrates after further addition of liquid, leading to a final increase of the power consumption curve, as the impeller blades start to chop the snow ball.

From the point of view of percolation theory, the wet agglomeration process can be considered as a ternary system, consisting of solid particles (A), of the granulating liquid (B), which occupies

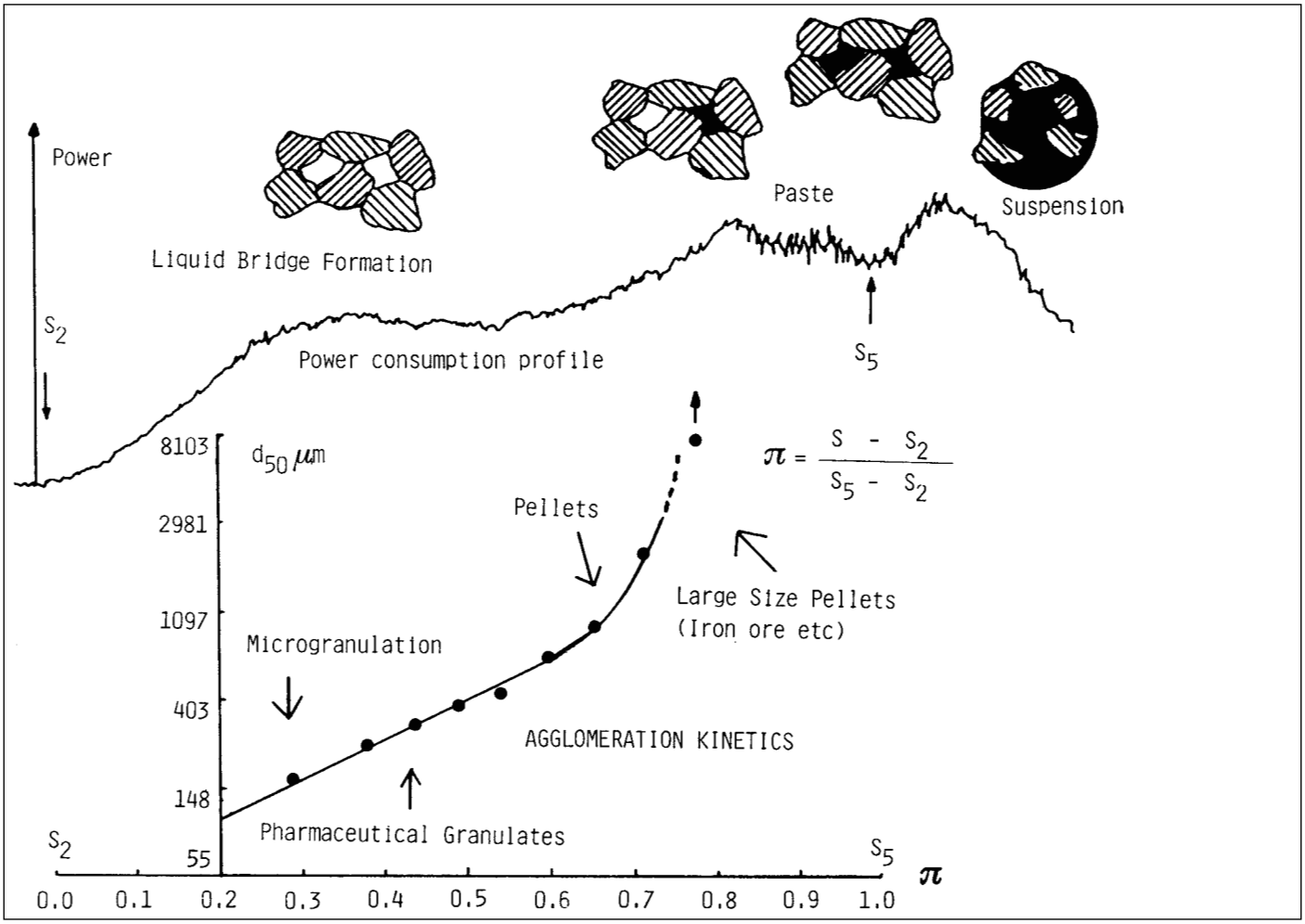


Fig. 9: Power consumption profile as a function of the normalized quantity π of the granulating liquid. The quantity π represents the degree of the filling of the void space between the particles during the formation of liquid bridges.

more and more the (gaseous) void space (C) between the particles to be agglomerated.

	Lower threshold		Upper threshold	
	Site	Bond	Site	Bond
Diamond	0.428	0.388	0.572	0.612
Simple cubic	0.3117	0.2492	0.6883	0.7508
BCC	0.245	0.1785	0.755	0.8215
FCC	0.198	0.119	0.802	0.881

Table 2: Site and Bond Percolation thresholds in 3D Lattices

Thus, the following lower and upper percolation thresholds (see table 2) can be expected and estimated as a function of π in Fig. 9:
Lower threshold π_{C1} = ca. 0.2–0.3,
The upper percolation threshold π_{C2} = ca. 0.7 – 0.8.
The practical experiment shows that only within the range of π = 0.3 and π = ca. 0.7 it is possible to manufacture pharmaceutical granules, which corresponds to the values S_3 and S_4 in the publication [3,4]. Above the upper percolation threshold, (π = ca. 0.7) the power mass is over-wetted, leading to a disaster. From the point of view of PAT (Process Analytical Technology) and "Right First Time", it is essential that the amount of granulating liquid is approximately equal to the mean one of the threshold values.

Effect of the amount of granulating liquid and the effect of the amount of drug substance: A striking analogy

Paracelsus (1493–1541) was the first to mention, that it is the dose, which matters, whether a drug substance will help or will be a poison. In fact, there is a striking analogy between the effect of the amount of a drug substance having a therapeutic window and the amount of a granulating liquid. Both substances react the same way: On the one side, there is no drug effect below the minimum effective plasma concentrationand on the other side, there is a minimum amount of granulating liquid needed, i.e. π_{C1} = ca. 0.2–0.3, to form pharmaceutical granules. Interestingly , if the amount of granulating liquid exceeds the upper percolation threshold, i.e. π_{C2} = ca. 0.7–0.8.,it is not possible to manufacture granules due to the overwetted powder mass. Again, in case of a drug substance with a therapeutic window toxic effects occur above a critical plasma concentration This analogy leads to the conclusion that percolation theory plays an eminent role in systems biology and treatment of patients (see chapter 4, Outlook).
Therefore, in order to avoid negative surprises, it is important to apply percolation theory at any time and to look for critical concentrations (percolation thresholds) not only in the case of the wet agglomeration process, but also in formulation research. Such a complex system like a formulation may behave completely different, below and above such critical concentrations. Unfortunately, a simple change in the particle size distribution or in the particle shape of the starting material can shift a percolation threshold to another concentration [17].

F-CAD* Module to predict power consumption profiles

CINCAP GmbH is actually modifying the core module of F-CAD in order to calculate the power consumption profile of a composition, which evolves during the wet agglomeration process. Thus, instead of calculating the amount of the drug, that is dissolved by the water bath as a function of time, F-CAD* calculates the number of liquid

bridges formed during the addition of a limited amount of water as granulating liquid. The first results look very promising, and lead to the conclusion, that the main contribution of the power consumption profile is due to the formulation and can be calculated using first principles. Then, in analogy to the determination of the dissolution rate profile, a corresponding calibration experiment takes into account the contribution of the equipment. This procedure was very successful in the case of F-CAD to take care of differences in the dissolution profile due to differences in the dissolution method (basket, paddle). An experimental reliable determination of the power consumption profile at least for the larger scale equipment is however a prerequisite.

2.5. Virtual Equipment Simulators (VES)

The details concerning the development of VES are documented in [9]. The aircraft industry has been using virtual training for pilots for decades (see Fig. 10).

Fig. 10: Today, pilots are trained using flight simulators [18].

Thus, the same procedure could be applied in the pharmaceutical industry: VES is an excellent tool for training the laboratory staff [18] on the large-scale equipment before manufacturing large batches. Thus, the frequency of human errors can be reduced.

For the benefit of finding relatively fast a solution to a burning problem, it is an advantage to combine F-CAD with the concept of VES. VES can include any type of equipment, i.e. not only equipment for manufacturing, but also for testing, analysing etc.

In addition, it is possible to collect extremely valuable information on the behaviour of the manufacturing equipment by data mining of numerous batch records in the manufacturing department. These data allow an optimization of the manufacturing process, and to establish correlations between the quality properties of the batches and the settings of the large-scale equipment according to the PhD thesis of Lars Rehorik [19]. Such data can be very helpful concerning "scale-up" exercises. The goal in this respect is the following: VES can mimic 1 to 1 the behaviour of small and large-scale equipment taking into account the physicochemical laws as described in [9]. Thus, the deviations from the principle of "self-similarity" (Buckingham's theorem [4]) may be compensated by quantifying the differences between small and large-scale equipment. The idea is to establish a "Transfer Function" between the settings of a small scale and large-scale equipment. It is important that such a transfer function is not only based on statistical correlations obtained from existing batch records. Unfortunately, false positive correlations exist much more than expected: a famous case is the correlation between the decreasing birth rate in the Alsace (close to Basel), being a well known home of many storks with its decreasing population. It is necessary that the transfer-function is supported by underlying physicochemical laws. It is needless to say that such an approach has many advantages, and would keep the flexibility of a company concerning the purchase of different equipments, i.e. the company would not be forced to adopt a very radical unified solution, i.e. to use at any time everywhere the same equipment.

3. Conclusions

A rigorous analysis of the scale-up process reveals that it is difficult to manufacture "right first time" small and large-scale batches. This is due to the lack of "self-similarity" of the equipment used. In this respect, the violation of Buckingham's theorem [4] creates hurdles. It is important to identify and to take care of these obstacles. In this respect, a computer-aided scale-up procedure can be very helpful Interestingly, "self-similarity" plays also an important role in formulation research: a robust formulation shows a batch-to-batch similarity. In case of formulations, dangerous hurdles are critical drug / excipient concentrations, which are often hidden. Such hurdles can be identified by the application of percolation theory. In this respect, the corresponding author is wondering why the concepts of percolation theory in the area of pharmaceutics [20] did not find so far a much broader application in industry and in academia. Just keeping in mind that such percolation thresholds (= critical concentrations) do exist is a key element for a better process and formulation understanding. Already the knowledge about the existence of critical concentrations in formulation should alert the responsible pharmacist, i.e. should induce headaches and insomnia. A quantitative treatment, using the basic equation of percolation theory, leads to impressive results and beautiful insights in the behaviour of a complex system:

$$X = S\,(p - p_c)^q \quad (1)$$

With X = property of interest, e.g. disintegration time t_d [17] of a tablet, S = scaling factor, p = concentration of the component of interest, e.g. disintegrant [17], p_c = critical concentration of the component, q = critical exponent. The existence of universally valid critical exponents [20] for a specific process in nature is an additional beauty with practical impacts. Such a quantitative treatment is very helpful in the interpretation of a "landscape" or "sensitivity" analysis of a formulation. The rigorous application of the concepts of percolation theory should boost the process and formulation understanding, which will facilitate the job by doing it "right first time".

F-CAD and VES are the tools of choice for a faster time to market and for obtaining a six-sigma quality. The proof of concept of virtual R&D, using F-CAD in the area of dosage form design and testing [9] allows an extension to pharmaceutical manufacturing, in order to implement a six-sigma performance. Companies applying this new approach will have an important competitive advantage.

The authors of this chapter are convinced that the replacement of the laboratory by *in silico* experiments is not limited to the design of classical solid dosage forms [9].
Both tools, F-CAD and VES have in common, to replace laboratory work by cheaper and faster *in-silico* work.
The success of F-CAD is a result of the *first principle approach,* i.e. of the use of cellular automata [9]. This procedure has its origin in nature. For a better understanding of formulations, it is mandatory to establish a "landscape", i.e. *"sensitivity analysis"*. In this context, it is necessary to apply percolation theory in order to be aware of critical concentrations, respectively percolation threshold, which may jeopardize the future product quality.
The principle of self-similarity is a key element in nature. Its violation is the origin of scale-up problems in the pharmaceutical industry. In this context, a corresponding Virtual Equipment Simulator (VES), mimicking small, and large-scale equipment can be very helpful and can be used as a valuable training tool.
The application of F-CAD and VES should lead to savings, which may exceed the results obtained in the aircraft industry [21].
Due to the fact that in many companies the departments are organized as independent profit centres, "kingdoms" are born which do not interact strongly enough for the benefit of the product. Thus, last but not least, the following comment for the introduction of a really rigorous "Right First Time"-concept may be the most important one: A company is doing best if all important players, independent of their department affiliation, give their best, like in a beautiful football match or soccer game of a world championship. It is needless to say that unfair players should receive the red card.

Fig. 11: A fractal fern, created by M. Puchkov.

4. Outlook

Interestingly, a formulation consisting of a drug substance and many excipients is already a complex system, but a manageable one. Such a system, which reacts with intestinal fluids, can be described in a retrospective way by classical mathematical models, differential equations etc. However, these classical models are not capable of providing any prediction in case of a completely new formulation. Why is this the case? Is it possible that classical mathematical tools are not appropriate for such complex systems?
The goal and beauty of physics is to find a simple, elegant analytical mathematical solution, explaining what happens in nature, such as Newton's law for the force F being F = ma, with m = mass and a = acceleration and/or Einstein's $E= mc^2$, i.e. a rather simple equation with incredible consequences.
However, some important physical laws of nature look only better if an appropriate system of coordinates is chosen. Sometimes a transformation of the equation into a more suitable, e.g. logarithmic space, may be also helpful.
Is it possible that the existing formalism of maths for achieving an analytical solution is not appropriate for natural complex systems? Studying percolation theory, it is surprising that percolation thresholds in three dimensions can only be calculated numerically, e.g. by means of the "Monte Carlo" method or by using cellular automata (C.A.). Interestingly, at the percolation thresholds, the principle of "self-similarity" plays an important role.
In nature, it is often possible to discover "self-similar" structures. The principle of "self-similarity" may play probably a decisive role in the evolutionary processes of life. Self-similar structures and fractal geometry have a lot in common, see [22] "Percolation Theory, Fractal Geometry, and Dosage Form Design" http://www.ifiip.ch/content/de/downloads/articles-download.html
The possibility, to create with simple rules complex patterns of nature, showing self-similarity is impressive and exciting (see Fig. 11, and see also
http://www.home.aone.net.au/~byzantium/ferns/fractal.html).
Ferns have been the favourite research topic of Nobel Laureate Tadeus Reichstein after his retirement from the University of Basel. He was always very modest and never arrogant. During the time, he was working at the University of Basel, he was doing research in very different areas. In addition to his work, which was awarded by the Nobel prize, he was the first to apply a biotechnological step in the synthesis of vitamin C, and it was not dishonourable for him to work also in the field of pharmaceutical technology such as freeze drying.
Due to the limited resources, universities have started to focus their research activities in areas which are in the trend [23]. Research papers in trendy areas have, indeed, a much better chance to be accepted for publication by the editors of Nature and/or Science. Consequently, there is a need of establishing a rank order of research fields, being promoted, or neglected. This is the most difficult task. In this context, there is a temptation to establish formal dogmatic rules based on existing common views such as that an applied research cannot be as good as a research work in a pure, fundamental research area. Such an idea is probably the origin of discussions in Germany and Switzerland whether it is possible to transfer the subject of pharmaceutical technology to the universities of applied science. Interestingly, on the one hand, industrial pharmacists usually graduate from a PhD curriculum which is by law not offered at the universities of applied sciences. On the other hand, the universities of applied sciences offer in Germany and Switzerland an excellent education for pharmaceutical engineers. Thus, the main goal should be to boost the cooperation between the two different institutions.
Fortunately, Swiss National Science Foundation and US Grant Agencies do not make a distinction: The grant applications need just the approval of the panels of the respective foundations, and it does not matter if it is pure or applied research, and if the scientist is or is not working at one of the top Swiss or US universities such as the Swiss Federal Institutes of Technology (ETHs), Harvard, MIT, Princeton etc. The topic of "Basic versus Applied Research"

was also part of a discussion between Tadeus Reichstein and Nobel Laureate Leopold Ruzicka, who was his mentor at the ETH Zurich. Leopold Ruzicka made the following clear statement: there is no distinction between pure and applied research, there is only good or bad research. Good research can be done with a molecule nobody is interested in, i.e., then, it is basic research. Good research can be done with a molecule of great societal impact, i.e., then, it is applied research.

Is a first-principle approach part of a basic or an applied research topic? It should not matter! The beauty of the first principle approach in the area of formulation research using cellular automata is its capability of wonderful predictions, such as the drug dissolution profile!

On the one hand, one has to be modest, as pharmaceutical formulations are complex, but not as complex as systems in the living nature. On the other hand, the discipline of formulation research may be an ideal playground for using cellular automata, and for preparing the grounds as an important tool in systems biology: Maybe, it will be possible to mimic *"in-silico"* biological cells, an assembly of cells, which interact with each other, or isolated organs etc., instead of creating harmful computer viruses. The authors of this paper have the idea that the strict application of the principle of "self-similarity" and the percolation theory [24] will be beneficial for the discipline of life science.

It is evident that living organisms need to contain "bio-switches", which allow to turn-on or turn-off a biological action. Thus, life is based on "bio-switches" being triggered by bioactive molecules, which can be divided in two classes:

1) An intrinsically active molecule "A" which is not toxic at higher doses. The molecules "A" may also interact with each other ("A"-"A").
2) A bioactive molecule "A*" which has an intrinsic toxicity, but in combination with a receptor molecule "B" leads to the desired biological action. In this context, the strength of the interaction "A*"-"B" (Lock and Key Model of Nobel Laureate Hermann Emil Fischer) plays a major role. The molecules A* may also interact with each other ("A*"-"A*").

The effects of "A" and "A*" can be discussed assuming the following, very simplified model of a "bio-switch" in an organism. The "bio-switch" can be physically imagined as a compartment, i.e. a box, which contains the molecules "B", the number of which is kept constant. The molecules "B" interact with each other ("B"-"B") and may play an active biological role.

The construction of the "bio-switch" allows to add now molecules of the type "A", respectively "A*" to this compartment, i.e. the number (amount) of the active molecules ("A", respectively "A*") in the compartment is slowly increased, keeping the amount of molecules "B" constant.

Then, the following behaviour can be observed:

- Case of molecule "A":

At a critical concentration, i.e. at the percolation threshold, "A" starts to percolate and initiates the biological action. Due to the lack of toxicity, only the lower percolation threshold can be observed. In fact, the compartment behaves similar to a powder mixture consisting of electrically conductive particles "A" and electrically non-conductive particles "B". The compartment becomes electrically conductive above the lower percolation threshold and keeps being electrically conductive.

- Case of molecule "A*":

The molecules of type "A*" will form a bond with "B" creating a new species "A*B". There will be an onset of the biological action as soon as the critical concentration has been reached (lower percolation threshold, see table 2). Above the upper percolation threshold the molecules "B" no longer percolate, i.e. the biological activity of "B" becomes jeopardized and adverse effects start to appear. If due to the continuous inflow of molecules of type "A*" all molecules "B" have been consumed, the remaining molecules "A*" will show their high toxicity, inducing severe toxic effects. Such a compartment model explains the existence of a therapeutic window.

These effects are related to the fact that there are two percolation thresholds in three dimensions.

Interestingly, percolation theory tells us that there is only one percolation threshold in two dimensions. Thus, the conclusion can be drawn that life can exist only in three dimensions! Such an idea is supported by Stephen Hawking who writes in his famous book "A brief history of time" [25] that life cannot exist in two dimensions, because an intestine to digest food would separate a living being into two parts.

Last but not least, the authors support fully the idea of Stephan Wolfram (Princeton University) that the application of cellular automata in biology is extremely exciting and a new kind of science [26]. Thus, the fundamental laws of systems biology may be written in the form of C.A.-codes and not as a set of differential and/or integral equations. The advent of relatively low cost high-performance computers will boost the research in this direction.

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Sterilitätstest-Isolator: Monitoring und Handschuhprüfung

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Die Europäische Pharmakopöe [1] fordert, den Sterilitätstest unter aseptischen Bedingungen durchzuführen: Dies kann entweder unter einer reinen Werkbank mit unidirektionaler Verdrängungsströmung, aufgestellt in einem Klasse B-Reinraum, oder in einem Isolator geschehen.

Das komplette Sterilitätstest-Isolator-System besteht aus der eigentlichen Isolatorbox (Modell Skanair) mit SPS-Steuerung (Siemens Simatec OP17), Steritest-Integralpumpe 316 II mit Fuss-Schalter (Millipore), Airsampler MAS 100 ISO (MBV), Waage, drei H_2O_2-Sensoren Polytron 2 (Dräger), PC (IBM, Betriebssystem Windows NT 4.0 mit Service Pack 5.0), 17-Zoll-Bildschirm (IBM), Farbdrucker (HP) und Monitoring-Software iFIX Version 3.5 (Intellution). Die Monitoring-Software iFIX erfasst die Daten, die in der SPS ausgewertet werden. Dazu gehören die H_2O_2-Konzentrationen (ein Sensor für den niedrigen Bereich bis 10 ppm, ein Sensor für den hohen Bereich bis 1000 ppm), Temperatur, relative Luftfeuchte, Differenzdruck, Geschwindigkeit der unidirektionalen Verdrängungsströmung, Verbrauch des H_2O_2 über die Waage gemessen, Betriebszeit und alle Alarmmeldungen. Der fest eingebaute Airsampler wird über eine eigene Software angesteuert. Das gesamte System wiegt ca. 900 kg. Bedienung und Wartung werden in [2] beschrieben.

Ausstattung

- 4 Handschuhe (Material aus H_2O_2- und Ethanol-resistentem Material)
- 1 Andockport mit Blinddeckel an der linken Seitenwand (Option für zukünftige Verfahrensweisen)
- 1 Anschluss für den Airsampler MAS 100 ISO an der rechten Seitenwand
- 1 Anschluss für einen Partikelzähler (optional) an der rechten Seitenwand
- 1 VHP-Sensor aussen (0,1–10 ppm) aus Arbeitssicherheitsgründen
- 2 VHP-Sensoren im Isolator (Messungen im niedrigen und hohen Bereich)
- 1 Steritest-Integralpumpe in der Mitte der Arbeitsfläche

Benötigte Materialien

- Wasserstoffperoxid 35%, H_2O_2, medizinisch rein, in 2,5 Liter-Flaschen
- Kontakt-Platten mit Caseinpepton-Sojamehlpepton-Agar, eingeschweisst in VHP-dichte Folie
- Petrischalen (d=90 mm) mit Caseinpepton-Sojamehlpepton-Agar für den Airsampler und zur Verwendung als Sedimentationsplatte, eingeschweisst in VHP-dichte Folie
- Steritest-Einheiten
- Flächendesinfektionsmittel
- Flasche für anfallende Spülflüssigkeiten
- Abfallbehälter für leere Ampullen und Vials
- Gestelle für zu prüfende Ampullen
- sterile Einmal-Handschuhe

Der typische Arbeitsablauf im Isolator gliedert sich in sechs Schritte:
1. Vorbereitende Arbeiten.
2. Beladen des Isolators mit den benötigten Proben und Materialien.
3. Dekontamination mit Wasserstoffperoxid.
4. Durchführung der Arbeiten zum Sterilitätstest.
5. Mikrobiologisches Monitoring während und am Ende der Arbeiten.
6. Entladen des Isolators und Nachbereitung.

Prüfung der Isolator-Handschuheingriffe

a) Visuelle Prüfung
Zu den vorbereitenden Arbeiten gehört, dass arbeitstäglich vor der Dekontamination eine visuelle Kontrolle der Handschuheingriffe, Stulpen und der dazugehörigen Verbindungen auf fachgerechten Sitz und auf Unversehrtheit durch entsprechend geschulte Mitarbeiter erfolgt. Dabei ist bei den Handschuhen besonders auf die Fingerkuppen und die Fingerzwischenräume zu achten. Das Ergebnis der Prüfung wird dokumentiert.

b) Dichtigkeitsprüfung mittels Skan-Prüfdeckel
Die Prüfung auf Dichtigkeit wird nach dem Druckabfallverfahren in Anlehnung an ISO 10648-2 („Containment enclosures – classification according to leak tightness and associated checking methods") ausgeführt.
Die Prüfung erfolgt wöchentlich. Dazu wird der runde Prüfdeckel mit dem Manometer (das Manometer Typ Minihelic II Gage von Dwyer Instruments Inc. wird jährlich kalibriert, Messbereich 0–1,0 kPa, Arbeitsbereich 0,5–0,9 kPa, Messtoleranz +0,05 kPa) in den Schultering des zu prüfenden Handschuheingriffs eingepasst. Danach wird die pneumatische Dichtung des Prüfdeckels auf einen Enddruck von 1,5 kPa aufgeblasen. Die Druckluftversorgung für den Testdruck wird an der dafür vorgesehenen Schnellverschlusskupplung angeschlossen. Der Handschuh mitsamt der Armstulpe wird langsam auf einen Starttestdruck von 0,9 kPa aufgeblasen (die Dauer der Druckaufgabe soll zwischen 0,5 min und 1 min liegen). Nach der Prüfdruckaufgabe wird sich nachfolgend ein langsamer Druckabfall bedingt durch die Ausdehnung von Handschuh und Armstulpe einstellen. Daher wird nachfolgend über einen Zeitraum von 2 min durch zweimaliges Nachblasen der Druck wieder auf den Startwert von 0,9 kPa eingestellt. Nach der Druckstabilisierung wird die Druckluftzufuhr entfernt und die Messung gestartet. Der Starttestdruck wird notiert, und über einen Zeitraum von 3 min wird pro Minute der Druck dokumentiert.

SOLL: Abnahme des Prüfdrucks < 0,1 kPa/min

Ein Druckabfall von > 0,1 kPa während der ersten Minute deutet auf ein undichtes System hin, entweder durch einen defekten Handschuh, Armstulpe oder durch einen fehlerhaft sitzenden Prüfdeckel.
Nach der Prüfung wird die Dichtung zum Schulterring durch Bedienen des Nadelventils entspannt und der Prüfdeckel wird abgenommen.

Massnahmen bei Nichteinhaltung der Spezifikation:

1) Eine erneute visuelle Kontrolle wird durchgeführt. Wird eine Leckage entdeckt, so wird das defekte Material ausgetauscht. Anschliessend erfolgt eine weitere Messung mit dem Prüfdeckel.
2) Bleibt die erneute visuelle Kontrolle ohne Befund, erfolgt eine zweite Messung mit dem Prüfdeckel. Entspricht der zweite Messwert ebenfalls nicht der Spezifikation, so müssen Massnahmen wie Handschuh- und/oder Armstulpenwechsel, Überprüfung des Prüfdeckels eingeleitet werden. Nach dem Wechsel von Handschuhen und Armstulpen muss eine erneute Messung erfolgen.

Mikrobiologisches Monitoring im Isolator

Vor Beginn der Prüfungen auf Sterilität wird eine Sedimentationsplatte im Isolatorinnenraum offen exponiert. Die Exposition läuft über die gesamte Zeit der praktischen Arbeiten der Sterilitätstests.
Nach Beendigung der Sterilitätstests werden mit insgesamt vier Kontakt-Platten Proben an den beiden benutzten Isolator-Handschuhen, an der Oberfläche der Steritest-Integralpumpe und auf der Arbeitsfläche des Isolators genommen. Ausserdem wird eine aktive Luftkeimsammlung mit dem Airsampler MAS 100 ISO durchgeführt; angesaugt werden 1000 Liter mit einer Geschwindigkeit von 0,45 m/s. Der Sammelkopf SH des Airsampler ist vertikal an der rechten Seitenwand des Isolators montiert. Der Sammelkopf ist autoklavierbar (15 min bei 121° C). Es ist vorher darauf zu achten, dass die Löcher im Siebdeckel des Sammelkopfes nicht verstopft sind. Der Start der Luftkeimsammlung kann manuell mit einem Fernbedienungsschalter oder direkt am Gerät erfolgen. Der Airsampler arbeitet nach dem Impaktionsverfahren und ist für Standard-Petrischalen ausgelegt.
Im Rahmen einer Behördeninspektion wurde angeregt, Partikelmessungen in das Routinemonitoring aufzunehmen. Partikel werden während der Erst- und Requalifizierungen gemessen, um die Reinraumklasse A im Isolator zu belegen [4]. Im Monitoring ist die Untersuchung der Luft auf Mikroorganismen mittels Airsampler aussagekräftiger und wichtiger. Eine Korrelation der Partikel- zur Luftkeimzahl ist bisher nicht belegt [3]. Eventuell vorhandene Partikel wären durch den (validierten) Dekontaminationszyklus steril und würden den Sterilitätstest nicht verfälschen.
Gemäss EG-GMP-Leitfaden [4] soll auch die Luftqualität des Raumes, in dem der Isolator steht, überwacht werden und für aseptische Verfahren zumindest der Klasse D entsprechen (aktives Air-Sampling: Warnlimit: 100 KBE/m^3, Aktionslimit 200 KBE/m^3). Die aktive Luftkeimsammlung wird arbeitstäglich in der Raummitte durchgeführt. Das monatliche Oberflächen-Monitoring umfasst Kontaktproben des Fussbodens und der Wände (Warnlimit: 100 KBE/25 cm^2, Aktionslimit: 200 KBE/25 cm^2).

Dokumentation

Die relevanten Isolator-Parameter werden von der Software aufgezeichnet. Am Ende des Isolatorlaufs werden die Daten mit einem Farbprinter ausgedruckt. Die Ergebnisse des mikrobiologischen Monitorings und der Handschuhprüfungen werden auf Formblättern notiert und zusammen mit obigem Ausdruck vom Operator und Laborleiter abgezeichnet und archiviert.

Abkürzungen

d Durchmesser
KBE Kolonie-bildende Einheiten
kPa Kilopascal (abgeleitete SI-Einheit des Drucks, 1 Pa = 1 N/m^2)
ppm parts per million
VHP vaporized hydrogen peroxide

Handschuh	1	2	3	4	Bemerkung	Datum	Sign.
	Druck [kPa]	Druck [kPa]	Druck [kPa]	Druck [kPa]			
Startwert	0,9	0,9	0,9	0,9			
1 min	>0,8	>0,8	0,75	>0,8			
2 min	>0,8	0,75	0,65	>0,8			
3 min	>0,8	>0,7	0,6	0,75			
entspricht ja/nein	ja	ja	nein	ja			
	visuell	visuell	visuell	visuell			
entspricht ja/nein	ja	ja	nein	ja	Loch in Armstulpe, nach Austausch Prüfung wiederholen		

Tabelle 1: Ergebnisse der Handschuh-Prüfungen (Druckprüfung sowie visuell)

Position	Aktionslimit	Ergebnis	Beurteilung: entspricht / entspricht nicht
Luftqualität			
Luftkeimsammlung	1 KBE/m^3		
Sedimentationsplatte	1 KBE/60 cm^2		
Oberflächenabklatsch			
Handschuh 1	1 KBE/25 cm^2		
Handschuh 2	1 KBE/25 cm^2		
Handschuh 3	1 KBE/25 cm^2		
Handschuh 4	1 KBE/25 cm^2		
Pumpe	1 KBE/25 cm^2		
Arbeitsoberfläche	1 KBE/25 cm^2		

Tabelle 2: arbeitstägliches Monitoring der Luft und der Oberflächen im Isolator

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SWISS PHARMA: Mehr als 30 Jahre im Gespräch mit der Pharmazeutischen Industrie der Schweiz – Live-Interviews der Jahre 1979 bis 2009

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 32. Jahrgang (2010) 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 gegen einen Unkostenbeitrag von CHF 50.– («Schutzgebühr») plus Versandkosten 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.

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