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# Impact of the digital revolution on the future of pharmaceutical formulation science

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ABSTRACT

The ongoing digital revolution is no longer limited to the application of apps on the smart phone for daily needs but starts to affect also our professional life in formulation science. The software platform F-CAD (Formulation-Computer Aided Design) of CINCAP can be used to develop and test in silico capsule and tablet formulations. Such an approach allows the pharmaceutical industry to adopt the workflow of the automotive and aircraft industry. Thus, the first prototype of the drug delivery vehicle is prepared virtually by mimicking the composition (particle size distribution of the active drug substance and of the excipients within the tablet) and the process such as direct compression to obtain a defined porosity. The software is based on a cellular automaton (CA) process mimicking the dissolution profile of the capsule or tablet formulation. To take account of the type of dissolution equipment and all SOPs (Standard Operation Procedures) such as a single punch press to manufacture the tablet, a calibration of the F-CAD dissolution profile of the virtual tablet is needed. Thus, the virtual tablet becomes a copy of the real tablet. This statement is valid for all tablets manufactured within the same formulation design space. For this reason, it is important to define already for Clinical Phase I the formulation design space and to work only within this formulation design space consisting of the composition and the processes during all the Clinical Phases. Thus, it is not recommended to start with a simple capsule formulation as service dosage form and to change later to a market ready tablet formulation. The availability of F-CAD is a necessary, but not a sufficient condition to implement the workflow of the automotive and aircraft industry for developing and testing drug delivery vehicles. For a successful implementation of the new workflow, a harmonization of the equipment and the processes between the development and manufacturing departments is a must. In this context, the clinical samples for Clinical Phases I and II should be prepared with a mechanical simulator of the high-speed rotary press used for large batches for Clinical Phases III & IV. If not, the problem of working practically and virtually in different formulation design spaces will remain causing worldwide annually billion of $ losses according to the study of Benson and MacCabe. The harmonization of equipment and processes needs a close cooperation between the industrial pharmacist and the pharmaceutical engineer. In addition, Virtual Equipment Simulators (VESs) of small and large scale equipment for training and computer assisted scale-up would be desirable. A lean and intelligent management information and documentation system will improve the connectivity between the different work stations. Thus, in future, it may be possible to rent at low costs F-CAD as an IT (Information Technology) platform based on a cloud computing solution. By the adoption of the workflow of the automotive and aircraft industry significant savings, a reduced time to market, a lower attrition rate, and a much higher quality of the final marketed dosage form can be achieved.



## 1. Introduction

Thanks to his broad academic education, a pharmacist is able to work in very different areas of the pharmaceutical industry, ranging from drug discovery, drug formulation of dosage forms, scale-up activities, production, conducting clinical trials to registration of a new medicine. In 2005 a working party of representatives from the pharmaceutical industry, the University of Basel (UB), and the University of Applied Sciences of Northwestern Switzerland (FHNW) studied the feasibility of a close cooperation between the Institute of Pharmaceutical Technology of the UB and the section of Pharma Technology of FHNW, responsible for the curriculum of a pharmaceutical engineer. In the report following the study (Leuenberger, 2005), the missions of both the industrial pharmacist and the pharmaceutical engineer were defined and survey was made, based on the evaluation of the Swiss

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Society of Industrial Pharmacists (GSIA), of the different fields of activities of the industrial pharmacist. The mission of the industrial engineer was defined as follows: *The pharmaceutical engineer must be able to convert pharmaceutical processes into technical installations and to operate them in a sustainable way*. In case of the industrial pharmacist the subsequent definition was found:

> *The industrial pharmacist is in charge of handling multi-disciplinary tasks such as dosage form design, pharmaceutical processes, analytical methods, biopharmaceutical-, quality-, patent- and regulatory aspects of the development and manufacturing of innovative medicinal products in order to successfully introduce them into the market in an efficient way, covering a broad range of job opportunities (Leuenberger, 2005).*

According to the survey of GSIA, the majority (19%) of the industrial pharmacists were working in the field of formulation development (pharmaceutical research and development), followed by the subsequent areas: pharmaceutical production (16%), registration (14%), marketing, sale, business development (12%), quality control, quality assurance (11%), analytical research and development (7%), Information Technology (IT), documentation, drug safety (6%), clinical research (3%), drug discovery (1%) and other areas (11%). The digital revolution will have an impact on all these areas.

The industrial pharmacist is predestined – as mentioned above – to work in all areas of the entire value chain from drug discovery, through analytical and pharmaceutical R&D, quality control (QC) and quality assurance (QA), production to registration. In this context, job rotations will contribute to improve the connectivity between the work stations (R&D, QA, QC, production, registration).

A lean and efficient IT (Information Technology) — system along the value creation chain starting from preformulation work to registration will facilitate putting together the documentation needed for registration and will help to optimize the connectivity of the value chain.

The following study is primarily related to the area of formulation science and specifically to the development of solid dosage forms. The development of an optimal i.e. tailor-made formulation requires excellent knowledge of the drug substance such as its physical–chemical and biopharmaceutical properties. In this context, a close cooperation between the industrial pharmacist and the people working in drug discovery is essential.

### *1.1. Drug discovery, the main focus of innovation in industrial pharmaceutical sciences*

Attempts to predict the future are in general limited to an extrapolation (Weibel, 2002; Leuenberger, 2015) from the past. This approach is usually applied to the growth of a market etc. For the following reason it is impossible to predict on this basis the future: an important scientific discovery may lead to a new disruptive technology that changes the future completely. A typical example for such a discontinuous development happened in the area of drug discovery, the primary field of innovation in the pharmaceutical industry: the discovery of restriction enzymes by Arber, Smith, and Nathans (Nobel Laureates in 1978) opened the field of a new class of drug substances, the biologics. Without the discovery of restriction enzymes the areas of recombinant DNA technology, biotechnology, genomics, metabolomics and proteomics would not exist today having a major impact on industrial pharmaceutical sciences.

The introduction of a new disruptive technology needs in general a decision of the top management, as in most of the cases such a technology cannot easily be integrated in an existing workflow. The discovery of a new biological drug with a high molecular weight and its development differ substantially from the discovery and development of small, low molecular weight molecules to be administered orally. The corresponding author of this contribution, who was working at Sandoz AG (now Novartis) after studying nuclear physics at the University of Basel, remembers well such a top down decision by the head of the Pharma Research Division. The success of biologics shows that the decision at the right time of the top management was both optimal and visionary.

New therapies and new drug substances will remain the major topic of innovation in pharmaceutical industry. An optimal drug discovery can be compared to finding a jewel, e.g. a diamond among the active pharmaceutical ingredients (APIs). The focus of this contribution is to show how the industrial pharmacist can apply formulation science in order to achieve the optimal performance of a new drug in a similar way in which cutting and polishing of a raw diamond will reveal its whole beauty and brilliance. In other words, what kind of formulation science needs to be applied to achieve six sigma quality, i.e., that the API shows optimal bioavailability, a minimum of side effects and its formulation exhibits an optimal robustness?

### *1.2. The task of formulation science and pharmaceutical technology*

Formulation of an API is defined by its composition and by the pharmaceutical processes to reach the goal of an optimal drug delivery system. Such a system can be compared with a vehicle of the automotive or aircraft industry, carrying the drug to its target in the body.

Depending on the route of administration, formulations cover a wide range of different vehicles, from liquid, semi-solid to solid dosage forms. These vehicles are known for centuries and no new types of vehicles have replaced the classical dosage forms.

Innovative new drug delivery systems are now becoming available due to advances in Nanoscience and Nanotechnology. However, such delivery systems are still in the research stage and have not yet achieved a breakthrough. The Food and Drug Administration (FDA) realized the impact of this emerging field and established a partnership with the Alliance for NanoHealth (ANH), comprising eight world established institutions, known as the FDA-ANH program (FDA-ANH program, 2015).

The earlier hype of transdermal therapeutic drug delivery systems (TTS) (Bracht, 2000; Gratieri et al., 2013) which were to replace oral dosage forms over time did not fulfill the expectations. On the other hand, liposomal formulations as new drug delivery systems were attracting a lot of attention in academia (Jamil, 2004; Fan and Zhang, 2013). Unfortunately, only a small number of liposomal drug delivery systems proved to be commercially successful. Thus, solid dosage forms such as capsules, tablets for immediate or controlled drug release represent the vast majority of drug delivery systems for oral administration of the market. This fact is linked to the convenience of administration and to the relatively low production costs.

The technology to manufacture capsules and tablets did not change fundamentally since its introduction. The formulation science of solid dosage forms was in the past mainly based on empirical knowledge and was considered as an art (Leuenberger and Lanz, 2005). Some processes have been poorly understood, leading to high batch to batch variability in the quality of the products. The mean quality of the marketed products corresponds to a 2 $\sigma$ quality with approximately 5% defective goods. For this reason, FDA started the Process Analytical Technology (PAT) initiative in order to improve the process understanding (Leuenberger and Lanz, 2005; FDA, 2015) and the product quality. The ultimate goal is to reach a world class, i.e. a 6 $\sigma$ quality of the products with practically no defective goods. In this context Benson and MacCabe (Benson and MacCabe, 2004) estimated worldwide losses of up to 91 billion $ (USD) in 2004 due to the lack of optimal product quality.

In spite of these big losses, research in the process technology for manufacturing optimal market ready dosage forms does not get the deserved attention in academia. Solid dosage forms such as tablets and capsules are considered to be obsolete in the academic research environment, which is understandable. However, the term formulation science covers not only the physical design of the drug delivery system but also the processes to reach this goal. Thus, *the primary task of the formulation scientist in academia is to perform research in new drug delivery systems and in new innovative process technologies.* As pointed out in the

study of Benson and MacCabe (Benson and MacCabe, 2004) it is necessary that the formulation scientist in academia should also do research in already marketed dosage forms. The originator industry has no time to do such studies. Research activities in academia related to existing but poorly understood classical dosage forms are ideal for preparing formulation scientists working later in the pharmaceutical industry on development of originator or generic drug formulations. Such research activities can be done as part of the curriculum of an industrial pharmacist preparing a master- or a PhD-thesis. Thanks to his diversified education the industrial pharmacist has an important role of accomplishing tasks at different work stations. To keep such an essential role, it is important that an IT (Information Technology) training is included in the future curriculum of the industrial pharmacist. For the industry it is essential, that a new type of drug delivery system needs to show advantages compared to existing ones regarding quality and cost of manufacturing. A typical example is the highly sophisticated oral osmotic pump drug delivery system (OROS) developed by Alza (Malaterre et al., 2009) for controlled release purposes, which is rarely used for new APIs due to its high cost. This fact leads to a simple law, which is highly respected in the pharmaceutical industry: cost of manufactured goods should be as low as possible without compromising the quality of the product. Thus *the primary task of the formulation scientist in the pharmaceutical industry is a service function to design and manufacture a dosage form with the optimal quality to serve best the biopharmaceutical requirements of the active pharmaceutical ingredient, i.e. the primary innovation.* In the best case the quality of the dosage form is increased while the cost for development and manufacturing of the drug delivery system are reduced. The goal of the formulation scientist in industry is to manufacture high quality formulations, i.e. to achieve quality by design (QbD).

## 2. Quality by design in industrial pharmaceutical sciences

### *2.1. ICH Q 8 R (2)*

The formulation scientist in industry is encouraged to follow the official guidelines set by the drug approval agency or by the international conference on harmonization of technical requirements for registration of pharmaceuticals for human use, i.e. ICH Harmonized Tripartite Guideline Pharmaceutical Development Q8 (R2) Current Step 4 version dated August 2009 (ICH Harmonized Tripartite Guideline (n.d.)). The results of a quality by design study can be summarized by surface response graphs in 3D or by contour plots (ICH Harmonized Tripartite Guideline (n.d.); Leuenberger, 1978; Leuenberger and Guitard, 1978) of the dissolution quality, e.g. 80% of drug dissolved in 30 min., as a function of two process parameters. The contour plots and graphs represent the design space exploration of the drug formulation as a function of the process parameters and of the composition. Thus, it is possible to estimate the effect of a change in quality of a specific excipient used, which usually corresponds to a quantitative change in the content of the specific excipient (Leuenberger, 1978). A flat response surface is an ideal case showing a robust formulation with low variability. In contrast, a rocky type of landscape, i.e. a mountain like the Matterhorn in Switzerland represents a non-robust formulation showing a high variability in the quality as a function of composition or process parameters. This kind of sensitivity analysis of a placebo, respectively model formulation was employed in the Pharmaceutical Development Department at Sandoz Basel in the late 1970s as reported by Leuenberger (Leuenberger, 1978; Leuenberger and Guitard, 1978) (see Fig. 1).

The idea behind this approach was to substitute a certain amount of filler excipient by the same amount of drug substance in order to analyze the subsequent effect on the quality of the formulation. This procedure is very time-consuming, labor-intensive, and requires a substantial quantity of drug substance (API), which is not available in the early development phase. Thus, the final dosage form for registration is often developed close to Clinical Phase IIc, where the attrition rate is lower than in Clinical Phase I (see Fig. 2). In such a case usually a simple capsule formulation as service dosage form is used for Clinical Phases I and II.

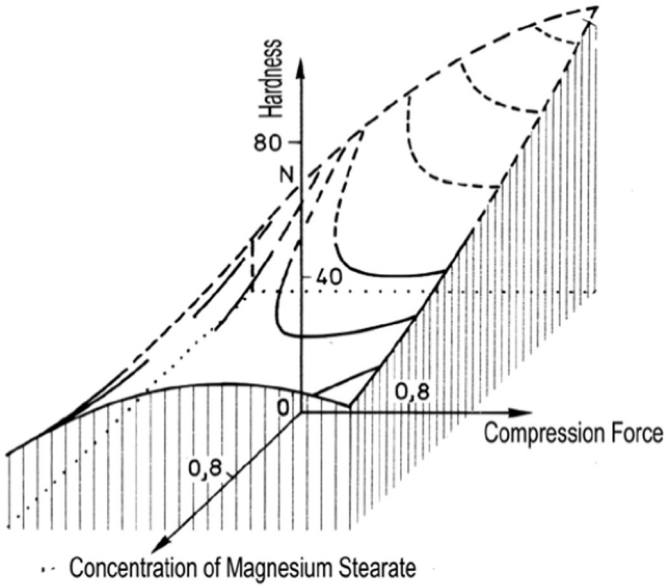


**Fig. 1.** Sensitivity analysis: response surface representation of the tablet quality parameter hardness as a function of the concentration of magnesium stearate and the compression force (Leuenberger, 1978; Leuenberger and Guitard, 1978).

### *2.2. Attrition rate of APIs during the different development phases and critical path initiative of FDA*

The high attrition rate in the different drug and drug formulation development phases are the result of the following three important complex factors: 1) safety, 2) medical utility, and 3) industrialization process, which is closely related to formulation science (see also Fig. 1). The three factors are graphically summarized in Fig. 3 of FDA's critical path initiative.

## 3. Clinical studies and formulation science

### *3.1. Net present value of an API during the different development phases*

Most important and most expensive are the clinical studies needed for the development of an originator drug substance. The authors thank Aylin Sertkaya et al. (Sertkaya et al., 2014) to use Fig. 4 and to refer to the study Examination of Critical Trial Costs and Barriers for Drug Development Final, which has been submitted to the U.S. Department of Health and Human Services, ASPE. Fig. 4 shows a typical example of an analysis of the net present value (NPV) of a specific API during the different development phases (Sertkaya et al., 2014). According to this study the following information has been provided for the analysis performed in Fig. 4 (Sertkaya et al., 2014): 1) Phase I trial is expected to cost $30 million and to require 100 participants to determine safety and dosage. This trial is expected to last one year and there is a 67% likelihood that the drug will successfully complete the first phase. 2) Phase II is dedicated to test the effectiveness of API in treating Indication X on 250 participants over a period of two years. This phase is expected to cost $45 million and the agent will need to demonstrate a statistically significant impact on a number of clinical endpoints to move on to the next phase. There is only a 41% likelihood that the drug will prove successful in treating indication X. 3) In Phase III, the testing will be expanded to 4000 patients.The phase will last four years and cost $210 million, and there is a 55% likelihood of success.4) Upon completion of Phase III, the sponsor will need to submit an NDA to FDA paying a user fee of $2 million and there is an 83% likelihood of being

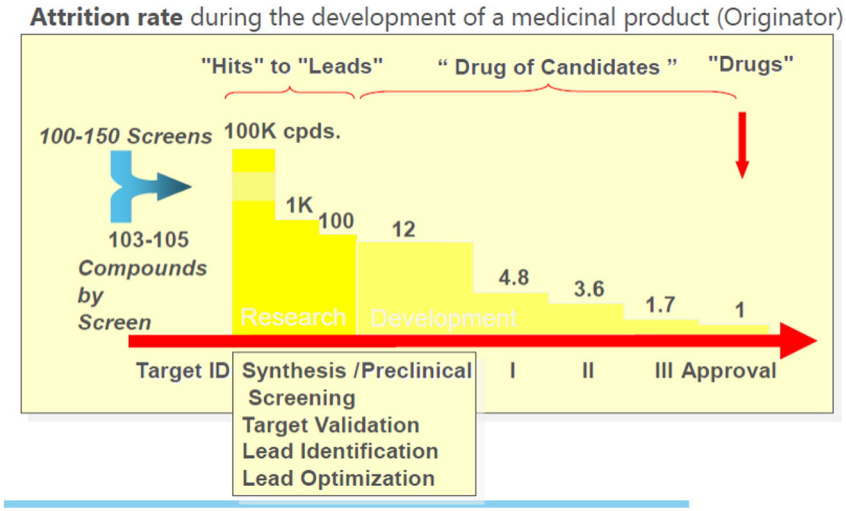


**Fig. 2.** Number (estimates) of promising APIs (drugs) in the pipeline of an originator company during the development phases. Preformulation activities for the development of a drug formulation start in the preclinical development, courtesy Dr. Ajaz Hussain, FDA.

approved.The NDA submission decision will take one year. 5) Given the size of the patient population and average wholesale price for similar drugs, the net revenue stream for the API, if it is approved, is estimated at $973 million over 15 years (Sertkaya et al., 2014).

The costs of the different phases depend on the indication and can vary very much, especially if the therapeutic effect requires a large size of participants to prove a statistically significant effect, such as in case of pain, anesthesia, and/or obesity. The average costs (in mio $) of clinical trials across indications (Sertkaya et al., 2014) are in the following range (mean ± standard deviation) for the different Clinical Phases: 3–5 (Phase I); 10–16 (Phase II); 12–28 (Phase III) and 5–35 for Phase IV (Sertkaya et al., 2014). It is evident, that the value of costs can be very different and depend on the specific API (see Fig. 4).

Due to the limited availability and high cost of the API in the early development phase, generally a simple service dosage form such as a capsule formulation is prepared for Clinical Phase I (see Fig. 5).

The final marketed dosage form is often a tablet formulation developed in Phase IIc. In this development phase the availability of drug substance is no longer a problem and the cost is much lower compared to Clinical Phase I. The transition from a capsule formulation to a tablet formulation requires a bioequivalence study, which is often a critical step being part of the critical path of the industrialization process (see Fig. 3).

### 3.2. Conventional workflow

Many pharmaceutical originator companies start with a service dosage form such as a simple capsule formulation for the first clinical study. However, due to regulatory issues it is not possible to change later fundamentally the composition of the service dosage form used in earlier clinical studies. For this reason, the degree of freedom for the formulation scientist is limited as a result of the limited size of the formulation design space. Thus, it is often extremely difficult on the basis of the composition of the early service dosage form, i.e. a capsule formulation, to reach a 6 σ quality for the final marketed tablet dosage form. The quality of the dosage form has a direct impact on the quality of the clinical trials: a high variability in the quality of the dosage form will lead to a high variability in the results of clinical trials. If at all the clinical study is successful, it will require a high number of patients to prove statistically a

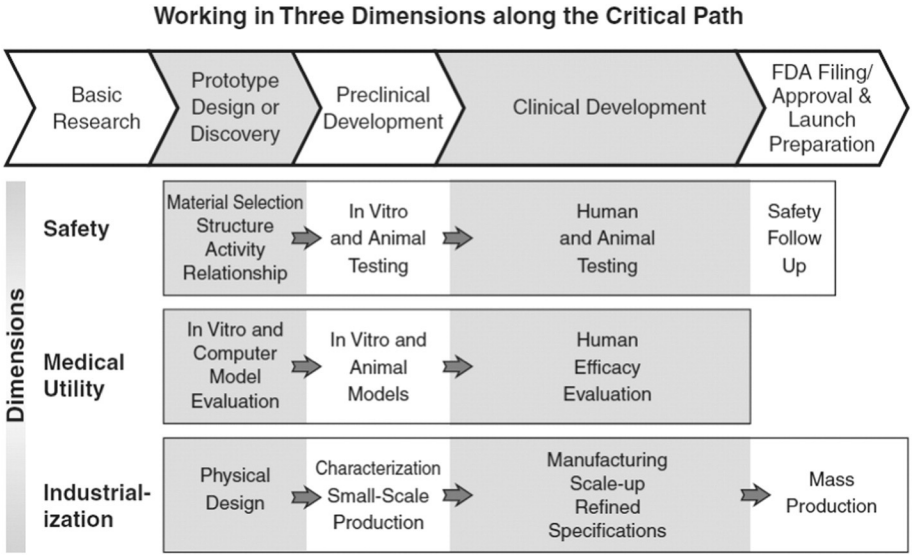


**Fig. 3.** Three dimensions of the critical path during the development of a new originator drug (Woodcock and Woosley, 2008).

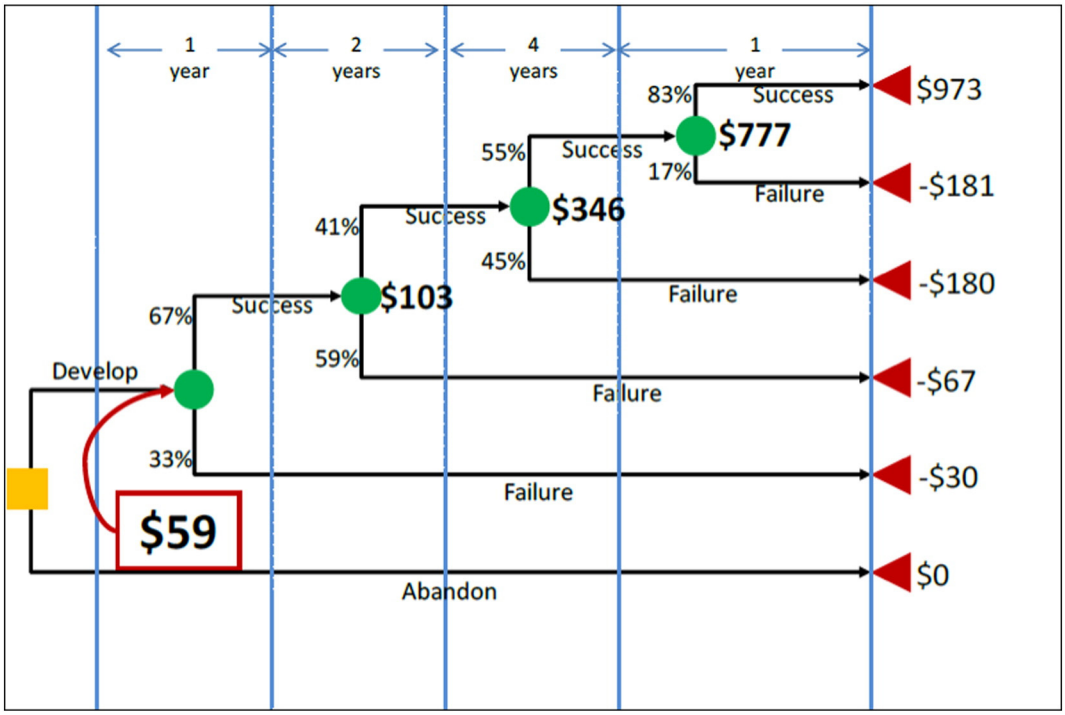


**Fig. 4.** Drug development decision tree depicting net present value (NPV) of returns at each node (courtesy of Aylin Sertkaya et al. (Sertkaya et al., 2014)). The yellow square corresponds to the initial decision to develop or to abandon an interesting active pharmaceutical ingredient (API). The $ figures in bold close to the green nodes are calculated from right to left, taking into account the probabilities of success or failure (in millions of $): $(973 \times 0.83) - (181 \times 0.17) = 777$. The costs of Phase IV are not taken into account.

significant effect. Thus, the quality of the formulation is a critical issue and has a significant impact on the length and costs of the clinical studies. Indeed, the losses in billions of $ published by Benson and McCabe (Benson and MacCabe, 2004) due to poor formulations and processes are not surprising.

## 4. The impact of the digital revolution on formulation science

Fig. 6 shows a selection of IT (Information Technology) software packages (Greb, 2013), which can be used to assist the formulation scientist with in silico modeling for an optimal development of a new medicament. Interestingly, there exists so far no software package (refered to as Holy Grail by Pfizer) which will cover the entire range starting with the properties of the API and ending at the in vivo performance of a drug formulation.

### *4.1. F-CAD, Formulation-Computer Aided Design*

The following discussion will focus on the software package F-CAD of CINCAP for the in silico modeling of a solid dosage form such as a capsule or tablet formulation for immediate or controlled release (Leuenberger et al., 2010; Leuenberger et al., 2013a; Leuenberger et al., 2009). F-CAD, i.e. Formulation-Computer Aided Design, is based on a cellular automaton approach, which allows a faster computation for the in-silico modeling of solid dosage forms compared to other approaches such as DEM/FEM (see Fig. 7 (Leuenberger et al., 2014)).

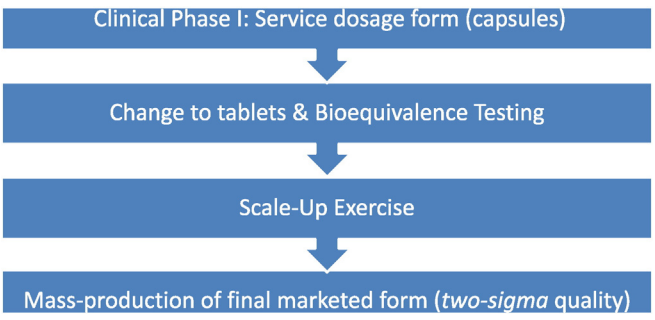


**Fig. 5.** Conventional workflow with a simple service dosage form for early clinical studies (Leuenberger et al., 2010; Leuenberger et al., 2013a; von Orelli, 2005).

For the application of F-CAD (see Fig. 8) it is important to know the physical–chemical properties of the drug substance and of the excipients used, which must be chemically compatible with the drug substance. The design of a solid dosage form formulation, i.e. a drug delivery vehicle, can be compared with the design of a car or aircraft carrying passengers. In the aircraft industry safety regulations are as important as in the pharmaceutical industry: the vehicle has to be constructed to be safe and this too applies to drug delivery system. The application of F-CAD has the great advantage making it possible to introduce the workflow of the automotive and aircraft industry in the pharmaceutical industry, i.e. the first tablet formulation corresponds to the first prototype of a vehicle or an aircraft. Like in the automotive and aircraft industry, the material used for the design of the vehicle has to be of highest quality. Thus, in case of a tablet formulation the properties of the excipients such as solubility, swellability, and compressibility must have a low variance. These properties of the excipients are generally known and are part of the parameters needed as input in the F-CAD software package.

It is important to note that for the application of F-CAD it is not necessary to know the chemical formula of the API, however the knowledge of the true density and the intrinsic dissolution behavior in a known buffer solution is absolutely required.

For a precise calculation of the drug release in a specific buffer solution of all possible formulations within the formulation design space as defined by ICH Q8 R(2), it is necessary to manufacture the tablet formulation with a minimal amount of drug substance using the recipe of F-CAD. This small laboratory batch has the important function of fine-tuning the parameters for the exact calculation of all possible formulations within the design space ranging from immediate to controlled

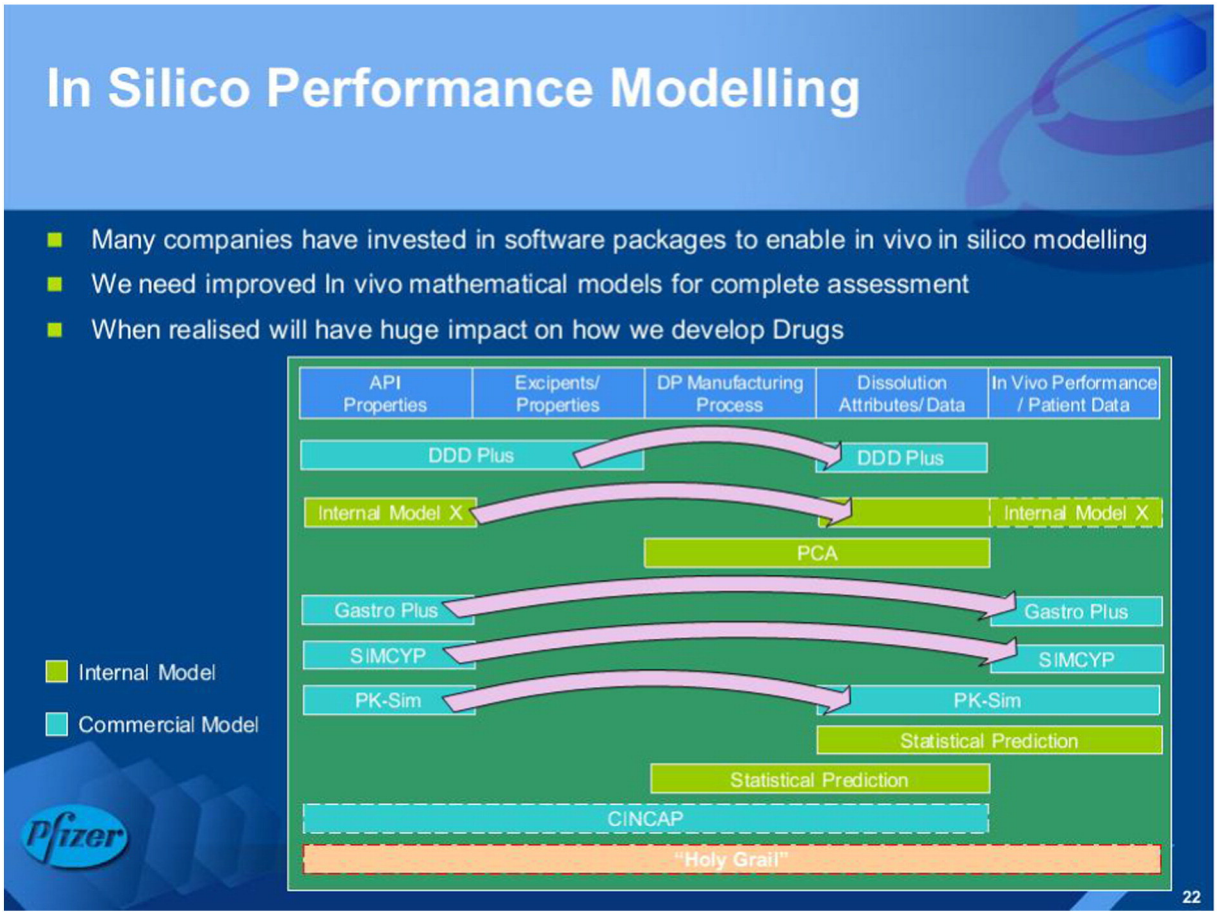


**Fig. 6.** Selection of software packages for in silico modeling, which can facilitate the task of formulation development (Greb, 2013).

release formulations. The fine-tuning is also necessary in order to take into account the type of in-vitro dissolution equipment, the type of buffer and its ionic strength (Krausbauer, 2009). In case of a very low soluble drug substance it is possible to add in the composition or in the buffer solution a solubilizer such as PVP (Leuenberger et al., 2013a) or Polysorbate 80 to form a complex or a micellar solution. In an extreme case of an insoluble drug substance it is also possible to use the disintegration time as a surrogate for the drug dissolution (Kimura, 2012). So far F-CAD was used mostly by industry for resolving difficult cases such as finding a tablet formulation with identical API in vitro dissolution profiles like the precedent capsule formulation to achieve a positive result in bioequivalence studies. Thus, proof of concept could be established (Leuenberger et al., 2010). Unfortunately, due to confidentiality agreements the detailed procedure cannot be published showing in most of the cases identical dissolution profiles with exceptions (see Leuenberger et al., 2013a). The exceptions are due to the limited

| Topic | CA-based models | DEM/FEM |
|---|---|---|
| Dissolution Simulation | yes | Yes |
| Swelling/diffusion | yes | Limited |
| Effect of granulation/milling | yes | Yes |
| Compaction Simulation | yes | limited |
| Memory usage | Extremely low | High |
| Particles per simulation | up to 1 000 000 000 | Ca. 1 000 000 max. |
| Calculation speed | Up to 250x faster than real experiment | Extremely slow (days for simulation) |
| Hardware costs | Moderate/Low | Extremely high |
| Usage complexity | Simple and straight forward | Special training is essential |

**Fig. 7.** Performance benchmarking of C.A. based models and standard modeling methods such as DEM (Discrete Element Method/Finite Element Method) (Leuenberger et al., 2014).

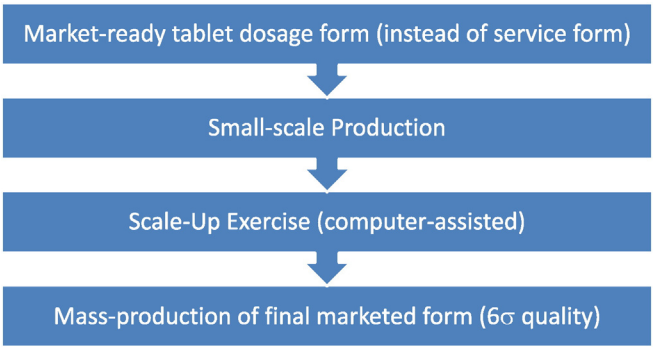


**Fig. 8.** "Right, First Time" workflow. Instead of a simple capsule formulation as service dosage form for the first clinical studies, the market-ready tablet formulation is prepared by F-CAD using the formulation design space according to ICH Q8 R(2) (Leuenberger et al., 2010; Leuenberger et al., 2013a).

formulation design space in a later stage of the development, i.e. that the composition cannot be changed in a major way due to regulatory issues. The calculation of dissolution profiles by F-CAD is explained in detail in the PhD thesis of Etienne Krausbauer (Krausbauer, 2009) and the estimation of the disintegration time of a low water soluble drug in the PhD thesis of Go Kimura (Kimura, 2012).I am thankful to my former PhD student Go Kimura, who introduced F-CAD within the Formulation Development Department of Shionogi to be used in the development of solid dosage forms (Kimura et al., 2013).Compared to the classical approach, which yields in general a 2 σ quality tablet formulation, F-CAD allows, thanks to the virtual design, a statistical quality-by-design approach which yields a top class 6 σ quality formulation (see Table 1 (Leuenberger et al., 2014)).

### *4.2. Digital revolution and the future of F-CAD*

The IT (Information Technology) or digital revolution is an ongoing process and affects our daily life using smart phones, smart watches, and smart tablets. Thanks to a secure cloud computing solution, the industrial pharmacists will use their smart phone or tablet to download new specifications of drug formulations. With the cloud solution the industrial pharmacist can rent at low costs F-CAD as a platform and as personal assistant in the daily laboratory work. Cloud computing is by definition a smart solution: you can sign up and rapidly start your F-CAD app as your personal assistant and advisor at any time in your lab or at home when having a new idea for an innovative formulation. No data are lost if your computer breaks down. The service is able to dynamically scale to the needs of the working station. Secure solutions are today available for software packages as a service (SaaS) or for a platform as a service (PaaS) using distant servers and high performance computers without the need of buying hardware and being responsible for its maintenance.

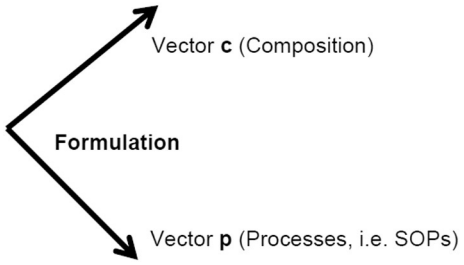


**Fig. 10.** 2D projection of the formulation design space.

## 5. Right, First Time workflow

The following "Right, First Time" concept and workflow are an attempt to adapt the workflow of the automotive and aircraft industry to the pharmaceutical industry using F-CAD as a tool.

The following topics illustrate the impact of F-CAD on the Clinical Phases I to III and on the submission of the NDA.

### *5.1. Impact of F-CAD on Clinical Phase I*

The goal of Clinical Phase I is to find the dose range of the API and to study its safety with healthy volunteers. Using F-CAD it is possible to design, develop and manufacture (see Section 4.1.) the final market-ready tablet dosage form already for the early Clinical Phase I.

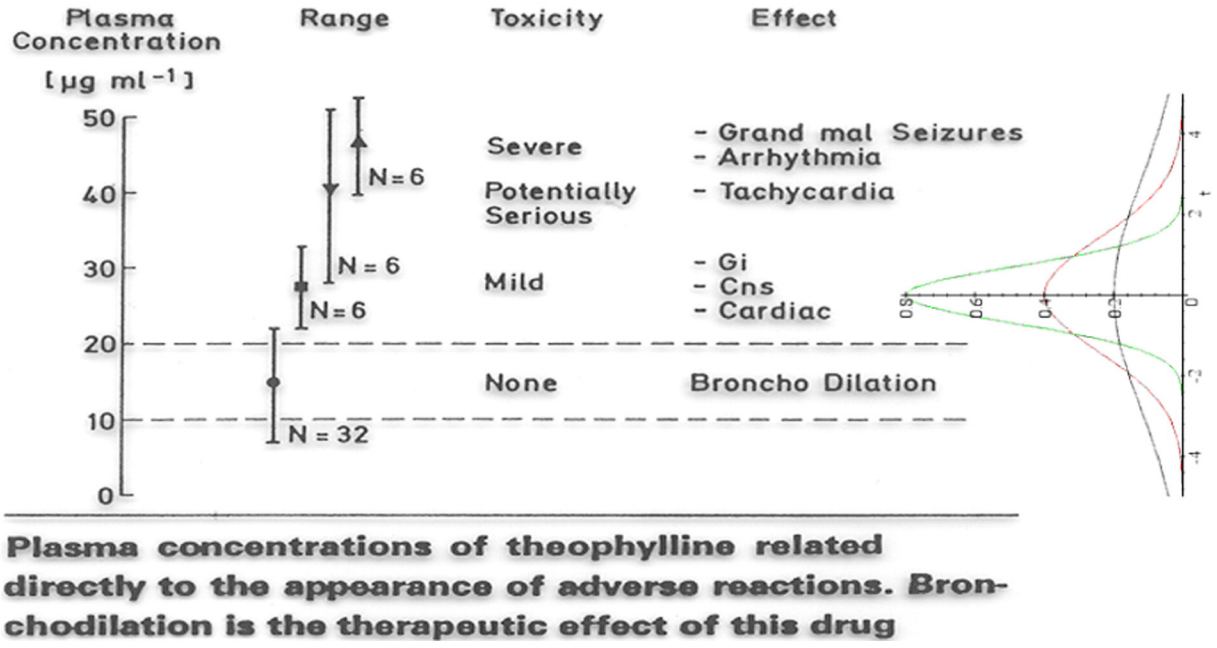


**Fig. 9.** Example of theophylline as a drug substance with a narrow therapeutic window (Leuenberger et al., 2014) .To detect a narrow therapeutic window with a tablet dosage form a six-sigma quality is mandatory.

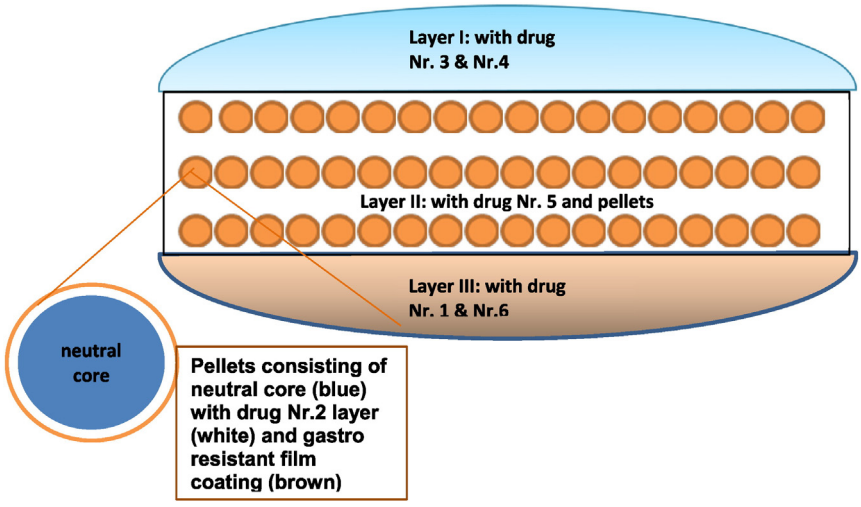


**Fig. 11.** Scheme of combi drug formulation with six different APIs prepared by Dr. Maxim Puchkov, Research Group Leader, Pharmaceutical Technology, University of Basel (Leuenberger et al., 2014). Layer I with 10 mg drug nr.3 and 50 mg nanomilled drug nr. 4; filler: 60 mg MCC with 5 mg AcDiSol as disintegrant; Layer II with 12.5 mg drug nr. 5 and coated pellets with 10 mg drug nr.2; cashion agent for the pellets: 120 mg MCC and 5 mg AcDiSol as disintegrant; Layer III with 10 mg drug nr.1 and 2 mg drug nr. 6; filler 132.5 mg MCC and 5 mg AcDiSol as disintegrant.

An in-silico sensitivity analysis similar to Fig. 1 will allow, with the help of F-CAD, to choose an optimal formulation for Clinical Phase I. Such an optimal and robust tablet formulation fully described within the formulation design space according to ICH Q8 can serve as a first tablet prototype to identify the right dosages, i.e. safe dosages without toxic side effects, and to perform an optimal ADME (Absorption, Distribution, Metabolism, Elimination) study in order to determine the oral bioavailability of the drug substance (see Fig. 9).

For safety purposes it is recommended to check initially not only the three different strengths, but also the two different drug release rates to study the influence of a fast and slow rise on the drug plasma level. Such a test is possible only because of the high quality of the solid dosage form with an extremely low variance of the defined drug dissolution rate. In general failure rates in Phase I are approximately 30% as a mean for all classes of drugs, i.e. antibody, peptide, small molecule, vaccine, etc. (Lowe, 2014).

The class of small molecules shows however the most brutal attrition rate in Clinical Phase I of ca. 92% (Lowe, 2014). It can be expected that the drug attrition rate will be significantly lower for a 6 σ quality formulation compared to a 2 σ quality service dosage form, especially for APIs with a narrow therapeutic window (see Fig. 9 (Leuenberger et al., 2014)).

The number of recruited healthy volunteers for this study should be kept in the normal range of 10–100.

**Table 1**
Quality by design can be realized better and cheaper using F-CAD by evaluating in silico the complete formulation design space.

| | Conventional production process | F-CAD |
|---|---|---|
| Sensitivity of formulation | Experience-based<br>A time-consuming and expensive collection of a huge number of laboratory tests. | Calculated<br>by integrated tests during the Virtual Integrated Design |
| PAT | Risk | Flexibility |
| Production process | Any deviation along the PAT registered production process<br>may cause a loss of batch | Process variability reduced since the quality of the final product is defined<br>since the start of Clinical Phase I |
| Quality | 2 σ | 6 σ |

### 5.2. Impact of F-CAD on Clinical Phase II

In Clinical Phase II the prototype tablet formulation is the first time administered to 100 to 300 patients in order to test efficacy using a pharmacodynamic study. Clinical Phase II can be subdivided in Clinical Phase IIa for conducting the proof of the concept with a smaller number of patients and in Clinical IIb to define the dose range for an optimal efficacy in treating patients. Failure rates in Phase II are in the range of 60% (Lowe, 2014).

Due to the better quality of the tablet formulation prototype, it can be assumed that the failure rate can be reduced to a lower percentage. For the same reason it should be possible to reduce the number of patients in this study by 10% as a conservative estimate.

In the case of the classical workflow with a simple capsule formulation as service dosage form, the development of the final marketed tablet formulation starts at the end of Clinical Phase IIb, i.e. in Phase IIc. But in case of the "Right, First Time" workflow, there is no need any more to develop the final marketed tablet formulation due to the fact that the final marketed tablet formulation is already well known from Clinical Phase I and Clinical Phase II. Thus, there is no need for bioequivalence study in Phase IIc between the earlier simple capsule formulation and the final marketed tablet formulation.

In addition, stability data for the market ready tablet formulation exist at room temperature since the start of the Clinical Phase I. Unnecessary work such as testing the stability of the capsule service dosage form, which is anyway of minor importance for the future NDA, can thus be eliminated.

### 5.3. Harmonization of processes and equipment: scale-up issues

The formulation design space (see Fig. 10) is defined by the excipients (composition vector **c**) and by the process parameters (process vector **p**). The multidimensional composition vector **c** includes the amounts (w/w) of drug substance and excipients with the condition that the sum of the components (weight fractions of API and excipients) = 1. Thus, $\mathbf{c} = (c_1, c_2, c_3, \ldots, c_{n-1}, c_n)$ with $c_1$ = amount of API (w/w), $c_2$ = amount of filler (w/w), $c_3$ = amount of binder (w/w), $c_4$ = amount of disintegrant (w/w), $c_5$ = amount of lubricant (w/w), etc. The process vector **p** includes as components SOPs (standard operation procedures such as the time of mixing the API and the excipients, the time of mixing the lubricant of the outer phase with the components

of the inner phase, the amount of granulating liquid used in the preparation of granules, the compression force, i.e. more specifically the distance between the upper and lower punch of a rotary press of a given formulation, etc.

It is important to keep in mind that the process vector **p** is usually very different from lab to lab and can vary in an important way during the scale-up procedure due to different equipment used. For this reason, the pharmaceutical company Sandoz (nowadays Novartis) harmonized the equipment at their different manufacturing sites (Leuenberger et al., 2010). A substantial part of the losses (Benson and MacCabe, 2004) due to problems of formulation and processes can be eliminated by the harmonization of the equipment.

In order to facilitate the scale-up process, we strongly recommend using a semi-continuous granulation process, which keeps constant the SOP and the equipment. This means that the labs in the early formulation department and the manufacturing department must use the same equipment. Thus, the geometrical dimensions (3D) of the equipment are kept constant and the scaling depends only on the 4th dimension, i.e. only on the manufacturing time (Leuenberger and Betz, 2011; Dörr and Leuenberger, 1998). For the same reason, it is highly recommended that in the pharmaceutical R&D labs special equipment for tableting is used, such as the "Presster" (Leuenberger et al., 2013a) for simulating mechanically the high speed rotary presses of the manufacturing department. In this way the process vector **p** can be kept constant.

In optimal case the clinical samples for Clinical Phase I and Phase II are manufactured with this special equipment. As a consequence, the results of the pharmaceutical tablet properties should comply with the results of the tablets of Clinical Phase III. Consistent results for Clinical Phases I–III will be supportive for the NDA submission. The scale-up of the pharmaceutical processes takes place in Clinical Phase III. Failures during the scale-up of large batches create unnecessary expenses and such large batches are not suitable for trial and error experiments Thus, it would be an advantage to offer to the formulation scientist an additional IT tool to test in silico the scale-up exercise. This task could be fulfilled by a Virtual Equipment Simulator (VES), which mimics the behavior of large scale equipment taking into account site specific differences. In this context, it is surprising that VES is not yet used in the pharmaceutical industry (Leuenberger et al., 2011) for training purposes, respectively as a tool for computer assisted scale-up.

Harmonization of the processes during scale-up includes the intensive use of PAT (Process Analytical Technology) devices, which can take into account specific properties of the primary material to be processed. In this context, the power consumption device, which was developed by Hans Leuenberger (corresponding author) in cooperation with Marcel Dürrenberger of the Engineering Department at Sandoz (Leuenberger, 1982), takes into account changes in the particle size distribution and of the moisture content of the primary material in order to control the wet agglomeration process. As a result, harmonization of the processes means that the settings of the high-speed tableting machines could be kept constant from batch to batch (Leuenberger et al., 2010). This was possible with the granulation control PAT device, which led to a reduction of the variability in the yield of the granule size distribution (see Table 2 (Leuenberger et al., 2010)). Without the PAT device the machine settings had to be adapted from batch to batch in order to get the same properties (hardness, disintegration time) of the resulting tablets.

**Table 2**
Harmonization of the wet agglomeration process with the subsequent tableting process by optimization and a significant reduction of variation of the % yield of the granule size distribution between 90 and 710 μm.

| Type of mode | % yield (**w**/w) 90–710 μm | % undersize (**w**/w) < 710 μm | %undersize(**w**/w) < 90 μm |
|---|---|---|---|
| Classical mode N = 20 batches (no PAT device) | 81.03 ± 2.42 | 88.30 ± 2.05 | 6.80 ± 0.51 |
| Automatic control (with PAT device) | 91.45 ± 0.36 | 96.80 ± 0.31 | 5.40 ± 0.35 |

### 5.4. Impact of F-CAD on Clinical Phase III

In Clinical Phase III failure rates are approximately 40% (Lowe, 2014). Clinical Phase III is the most important and most expensive clinical study with the goal to demonstrate the medical utility of the new drug substance compared to a placebo or to the "gold standard" formulation of a competitor drug substance on the market. For marketing strategies of a new medication it is important to know very well the drug and the drug formulation of the competitor. Such a comparative investigation has to be a double-blind study, which is a challenge for the formulation scientist: in the ideal case the new originator drug formulation, such as a tablet, needs to look identical to the gold standard formulation of the competitor.

Employing the classical workflow, it is in general too difficult to achieve this goal: in order to create a double-blind study of two different tablet formulations with identical dosage forms, the two tablets are usually milled separately and filled into identical capsules, thereby checking that the dissolution rates of these capsule formulations correspond to the respective tablets. In some cases, it is possible to hide the tablet of the competitor and the new test tablet in separate identical capsules. However, in certain countries the patients may open the capsules for inspection, and if a difference in odor or content becomes evident, the goal of the double-blind study is lost. Thus, it is not surprising that the results of the studies in Clinical Phase III are not easy to interpret and can become lengthy due to the need of a larger number of patients.

In the optimal case, the tablet formulation of the new drug should look identical to the tablet formulation of the competitor. This goal can easily be achieved at reduced cost by using F-CAD and also by performing the formulation sensitivity analysis for the preparation of the market-ready tablet formulation already in Clinical Phase I. Thus, an originator tablet formulation having the identical shape and volume of the competitor formulation can be prepared for the double-blind study. Due to the higher quality of the F-CAD drug formulation compared to the competitor drug formulation on the market, the results of the Clinical Phase III studies should require a smaller number of patients to obtain significant results. If the drug formulation of the competitor drug is not optimal, it may be of interest to establish a drug formulation sensitivity analysis according to ICH Q8 R(2) in order to understand better the behavior of the competitor drug. If the drug substance of the competitor is easily available, there is no problem to do such a formulation sensitivity analysis at low costs thanks to the capability of F-CAD to perform reverse engineering (see the following Section 6: Generics and Combination Drug Formulations).

## 6. Generics and Combination Drug Formulations

### 6.1. F-CAD and generic formulations

F-CAD is an ideal tool for developing generic formulations due to its reverse engineering capability. In several countries, such as Belgium, the regulatory authorities need to know qualitatively the composition of a dosage form since some patients may show allergies to a specific excipient used in the drug formulation. The dissolution rate profile in a specific medium of an originator tablet formulation can be easily measured. From the knowledge of the dissolution rate profile and the excipients of an originator product, F-CAD can calculate the amount of the different excipients in the originator formulation and can establish a sensitivity analysis by exploring the formulation design space. Special attention has to be paid to the equipment used for scale-up reasons (see Section 5.3.).

Thus, with the help of F-CAD, the industrial pharmacist can explore the formulation design space using the standard operation procedure (SOP), i.e. to focus on the formulation design space of the composition. The sensitivity analysis of the composition with a given lab SOP shows the available degrees of freedom and the robustness of a given formulation. The degrees of freedom are important in order to be able to identify a formulation of the chosen API, which is out of patent protection and which is different from the originator formulation, which may be still under patent protection. The formulation sensitivity analysis of the formulation of a competitor product may also be of interest for an originator company to know the positive and negative features of the competitor formulation on the market. For a generic company the problem is also that the copy of the competitor formulation is not allowed to be pharmacologically better, such as showing a better bioavailability, but has to be as good or as bad as the branded originator product in order to avoid costly additional clinical studies. Thus, the primary goal is a positive result of the bioequivalence study.

### 6.2. F-CAD and bioequivalence studies

So far F-CAD has been primarily used for bioequivalence studies such as in the case of generic formulations in order to be rendered equivalent with the originator formulation or in the case of conventional workflow of originator products in order to change the formulation from a simple capsule to a market-ready tablet dosage form. This laboratory work showed excellent proof of the concept of F-CAD using standard operation procedures combined with a calibration experiment (see Section 4.1.) for manufacturing tablets or capsules (Leuenberger et al., 2010).Thus, it is possible to calculate in the design space with a high precision formulations, which are located far from the neighborhood of the lab tablet formulation used for calibration purposes without the need to validate experimentally each in silico formulation in the formulation design space. However, it has to be kept in mind that the standard operation procedures for manufacturing of the two formulations to be tested do not differ too much, i.e. that the process vector **p** of each formulation is more or less identical. In other words, if for both the originator product and the generic version a wet granulation procedure is used, then this condition is in general fulfilled. Smaller differences in the equipment can be compensated by smaller changes of the composition vector **c**, provided they are within the composition design (sub) space. Such a compensation is usually not possible if the originator product is manufactured e.g. by a roller compaction process and the generic formulation uses a wet granulation process. Due to important differences in the process vector **p** there is a possibility that the bioequivalence study between a simple capsule formulation and a tablet formulation will fail, because for first-principle reasons it is not possible to design the formulation without changing fundamentally the composition. In other words, it is not possible to use additional excipients, that the tablet formulation will show an identical dissolution profile like the capsule service dosage form. Because of regulatory issues a fundamental change of the composition during the clinical trials is too risky and may lead to the request to repeat earlier clinical studies with the same composition. Such a situation is not uncommon and leads to costly and lengthy extensions of clinical studies contributing to the losses as reported by Benson and MacCabe (Benson and MacCabe, 2004).

### 6.3. F-CAD and Combination Drug Formulations

A presentation by H. Leuenberger (the corresponding author) at the 5th Pharmaceutical Technology Conference in Tokyo (Kawashima, 2014) with the theme "Trends in Pharmaceutical Technologies with the Focus on Solid Dosage Forms", November 27, 2013, was focused on F-CAD since a Japanese pharmaceutical company is already using the F-CAD platform. Japan has the highest percentage of people with age over 100 years, i.e. has a high percentage of elderly people using four or more different medications three times a day. As discussed during the conference patient compliance can become a difficult problem, which could be resolved by combining drug formulations. In this context F-CAD is an excellent tool for the design of Combination Drug Formulations if drug-excipient compatibility studies of the drugs involved are known (Leuenberger et al., 2014).

Thus, F-CAD will facilitate the development of combination drug formulations, which opens an interesting market, especially for generic companies to fulfill the needs of the elderly generation and to avoid problems with polypharmacy.

When no Combination Drug Formulations are available on the market, it is a common practice that the responsible person in retirement- and nursing-homes prepares the poly medication (up to more than 10 different drugs) for the elderly people, which is time-consuming and may lead to mistakes. In Switzerland this service is provided by retail pharmacies, whereby the individual medications are prepared in plastic bags for patients in retirement homes.

The idea to prepare Combination Drug Formulations is strongly supported by FDA: Janet Woodcock, Director of the Center of the Drug Evaluation and Research, sent to the corresponding author the following comment after having read the content of Fig. 11: *Wow, very interesting. Getting to single tablets for the elderly (and others) will require this sort of dosage/manufacturing flexibility. Hope you get uptake*!! (Woodcock, 2014).

In addition, Janet Woodcock mentioned that combination drugs are also important for the younger people.

## 7. Conclusions

### 7.1. Drug discovery

Most exciting and most innovative task of the pharmaceutical industry is the discovery of a new drug substance, an API (NCE or NME) capable of curing an illnesses or of relieving severe symptoms, in other words to find a new therapy and to put a new medication on the market. A safe application of the API is a prerequisite and requires careful toxicological studies. Safety and medical utility issues are part of the critical path in introducing the new therapy on the market (see Fig. 3). Both safety and medical utility are intrinsic properties of a new API, which are given and are result of its chemical structure.

### 7.2. Clinical studies and formulation science

The issues of safety and medical utility of an API need to be carefully evaluated during the clinical trials. Thus, finding the dosage range and determination of the therapeutic range in Clinical Phase I and Clinical Phase II are of utmost importance. For this reason, the industrialization process, the third critical path (see Fig. 3) being a service function for the API, requires full attention: it is the job of the industrial pharmacist to develop an optimal formulation, which shows the beauty and covers the ugly parts of an API with the goal to develop a tailor made formulation with 6 σ quality already in Clinical Phase I. Clothes make people: nowhere is this saying more appropriate than in the business world. Special attention has to be paid to APIs with a narrow therapeutic range (see Fig. 9). The industrialization process, especially the part of formulation, is the only critical path which can help to reduce the attrition rate in the different clinical phases and the billion dollar losses reported in the study of Benson and McCabe (Benson and MacCabe, 2004). These unnecessary costs contribute to the annually raising R&D costs of putting a new medication on the market.

### 7.3. Adoption of the workflow of the automotive and aircraft industry

For this reason, it is important that the industrialization process is streamlined. In an ideal case the optimized industrialization process will lead to products of a higher quality at lower costs. Such an opportunity is given by introducing the workflow of the automotive and aircraft

industry in the pharmaceutical industry with the help of F-CAD of CINCAP or with another appropriate software platform capable of designing in silico formulations. The cost savings, which can be obtained during the clinical phases, are conservative estimates and can be substantially higher depending strongly on the individual properties of the respective API. Due to the use of F-CAD the amount of lab work in the formulation department will be substantially reduced since only a limited number of in-silico formulations need to be validated. This concept enables development of the market-ready tablet (or capsule) formulation with 6 σ quality and at low cost already for the Clinical Phase I. All the technical and medical data obtained with the tablet formulation during Clinical Phases I and II will help conducting high quality clinical studies in Phase III.

### *7.4. No need for a simple capsule service dosage form for Clinical Phase I and Phase II studies with the new "Right, First Time" workflow*

A cheap and low quality capsule service dosage form for the Clinical Phases I and II studies, the development of the final marketed tablet formulation in Clinical Phase IIc, and a subsequent bioequivalence study are no longer required. Thus, the adoption of the concepts of the automotive and aircraft industry will lead to a streamlining of the current workflow in the pharmaceutical industry, which will lead to additional savings of the same magnitude as the conservative cost reduction estimates in Clinical Phases II and III. This "Right, First Time" workflow was first published in SWISS PHARMA in English (Leuenberger et al., 2013a) and later in PHARM TECH JAPAN in Japanese (Leuenberger et al., 2013b; Leuenberger et al., 2013c). Dr. Janet Woodcock, Director of the Center of Drug Evaluation and Research at FDA, commented the article in SWISS PHARMA in a personal communication to the corresponding author as follows: *Thank you very much for sending me your provocative article on right first time. It is very timely and I certainly hope we will see widespread adoption in industry. I'm not sure many in industrial pharmacy are aware how predictive in silico approaches have become. FDA is certainly supportive* (Woodcock, 2013).

### *7.5. Generic solid dosage forms*

For Generic companies the application of the F-CAD platform is the tool of choice to explore the formulation design space of originator products. This knowledge enables a fast development of any generic formulation and will facilitate the necessary bioequivalence studies. There is no need for a major change of the current workflow in a Generic company by using F-CAD. Morover, F-CAD has the advantage that there is no principal or time difference between developing an immediate release or a controlled release formulation.

### *7.6. ICH Q8 R(2) guidelines and the choice of a capsule or tablet formulation*

According to the ICH Q8 R(2) guidelines the formulation design space is defined by the composition and the processes involved in developing and manufacturing a solid dosage form. In the rigorous description of mathematics this formulation design space consists of the two vectors $\mathbf{c} = (c_1, c_2, c_3,\ldots, c_n)$ representing the composition and $\mathbf{p} = (p_1, p_2, p_{3,\ldots}, p_n)$ representing the processes (see Fig. 10). For this reason, the design space for a capsule dosage form is by definition disjoint from the design space of a tablet formulation since the spaces do not overlap and have in common only the vector **c** (composition). Due to this fact, the policy to start with a simple cheap capsule formulation as a service dosage form and to change later to a tablet formulation is from a rigorous point of view (set-theory) completely wrong.

Thus, the responsible team should decide before starting the first clinical trials whether the final dosage form should be a capsule or a tablet formulation. Using the "Right, Fist Time" workflow it is important that the formulation design space for the final marketed capsule or tablet formulation is explored to evaluate in silico the optimal dosage form.

### *7.7. Bioequivalence studies*

According to the conclusions of Section 7.6., it is impossible to create a tablet dosage form with exactly the same properties as the service capsule dosage form, which has been already tested. This does not mean that a tablet dosage form will never be bioequivalent with the capsule formulation. However, it may be difficult to obtain exactly the same dissolution profiles for the different dosage forms. Therefore, bioequivalence studies can become a hurdle and thus, it would be better to choose the desired dosage form from the very beginning before starting Clinical Phase I (see Section 7.6).

### *7.8. Modernization and harmonization of the equipment*

In an optimal case the small tablet batches for Clinical Phases I and II are manufactured in the same way as the tablets to be compressed later on a high speed tableting machine in the manufacturing department. Today this is possible by using special equipment which simulates mechanically a high speed tableting machine. It is self-evident that the equipment at the different manufacturing sites of one company should be harmonized, i.e. be identical, in order to avoid differences in the product properties and qualities. The introduction of the workflow of the automotive and aircraft industry, using Computer Aided Design in formulation science together with a harmonization of the pharmaceutical equipment and processes will significantly reduce the losses mentioned in the study of Benson and MacCabe (Benson and MacCabe, 2004). In this context, preformulation studies with the goal "prevention is better than expensive repair actions" should not be limited to a chemical API-excipient compatibility program (Leuenberger, 1975) but should include as well a specially designed galenical API-excipient screening program (Leuenberger (n.d.)) for an early detection of interactions. It has to be kept in mind however, that the best in-silico platform will not help if the harmonization of the equipment and of the processes is neglected.

### *7.9. Next steps*

The full implementation of the new workflow of the automotive and aircraft industry for small API molecules and the harmonization of the processes/equipment for eliminating the problems of the industrialization process as a critical path according to Fig. 3, will need a decision at the top pharma management similar to the decision to bring biologics to the market following the Biotec Revolution. A special working party needs to study carefully the needs for introducing successfully the workflow of the automotive and aircraft industry. This task includes the evaluation and validation of the F-CAD software platform, to establish a decision tree for selecting the appropriate formulation design space according to the results of preformulation studies. The formulation design space for manufacturing samples for Clinical Phases I–III needs to cover in-silico and laboratory validation experiments, which is anyhow a prerequisite. Last but not least this study has to put a special emphasis on the harmonization of processes and of the equipment to avoid subsequent scale-up problems. As an important spin-off of this study an intelligent and lean IT management information/documentation system will result, which will facilitate the industrialization process from Clinical Phase I to registration.

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