# Project-, Drug-, and Business Development in a Biotech SME

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For MM, WP & Achim

*"Drug development requires some inspiration, a lot of perspiration, and rational planning"*
- D. Hal, CEO of FlexiMab Inc.

"The intuitive mind is a sacred gift and the rational mind is a faithful servant"
- Albert Einstein

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## List of Terms and Abbreviations

| | |
|---|---|
| AA | Accelerated Approval |
| AdBoard | Advisory Board |
| ALL | Acute Lymphocytic Leukemia |
| AMG | German Medicines Act |
| ASCO | American Society of Clinical Oncology |
| ASH | American Society of Hematology |
| ATU | Autorisations Temporaires d'Utilisation |
| BD | Business Development |
| BLA | Biologic License Application |
| CA | Competent Authority |
| CAGR | Compound Annual Growth Rate |
| CHMP | Committee for Human Medicinal Products |
| CMC | Chemical Manufacturing & Controls |
| CNS | Central Nervous System |
| CTA | Clinical Trial Application |
| eCTD | Electronic Common Technical Document |

| | |
|---|---|
| eDMS | Electronic Data Management System |
| EMA | European Medicines Agency |
| EoP2 | End of Phase 2 |
| EU | European Union |
| FDA | Food and Drug Administration |
| HTA | Health Technology Assessment |
| IB | Investigator Brochure |
| IMP | Investigational Medicinal Product |
| IND | Investigational New Drug |
| IQWIG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen |
| MA | Marketing Authorization |
| MAA | Marketing Authorization Application |
| mAB | Monoclonal Antibody |
| MAH | Marketing Authorization holder |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MoA | Mode of Action |
| MRD | Minimal Residual Disease |
| NDA | New Drug Application |
| NCE | New Chemical Entity |
| NHL | Non-Hodgkin Lymphoma |
| NPV | Net Present Value |
| ODD | Orphan Drug Designation |
| PDCO | Pediatric Committee |
| PEI | Paul-Ehrlich-Institut |
| PIP | Pediatric Investigation Plan |
| PPS | Pentosan Polysulfate Sodium |
| QA | Quality Assurance |
| RA | Regulatory Affairs |
| RCT | Randomized Controlled Trial |
| RMP | Risk Management Plan |
| SA | Scientific Advice |
| SAE | Serious Adverse Event |
| SAT | Single Arm Trial |
| SmPC | Summary of Product Characteristics |
| SPA | Special Protocol Assessment |
| TPP | Target Product Profile |

## EXECUTIVE SUMMARY

This thesis highlights the Project-, Drug-, and Business Development process of a hypothetical biopharmaceutical company advancing an anticancer platform based on a new antibody design.

The objective is to present some decisive steps and gate controlled decisions in setting the course for development and to put it in the context of the existing regulatory framework. The rational why and how specific decisions are made is presented. The topics are embedded in a storyline and illustrated as case studies[i] with an emphasis on the management of risks.

## INTRODUCTION

During the last 10 years of the past century, there was a hype for investments in telecommunications, internet, renewable energies, and biotechnology - the so-called "New technologies".

For small biotech companies the window of opportunity was wide open and in many cases money was invested in nothing more but ideas without any proof of concept. Even venture capitalists invested fortunes without fundamental knowledge of this industry.
Moreover, also amateur investors suddenly became players and in order to attract money to the stock market it was sufficient to use buzzwords such as "genomics", "bio", or "life sciences" in company names. Even so, this kind of investment behavior was rewarded for quite some time and many investors made considerable amounts of money just by buying biotech pre-IPO shares.

However, Biotech represents an expensive, high risk, and long-term investment and the business model of a typical former early-stage drug discovery firm without any revenues was a gamble. It was a binary all-or-nothing approach: succeed with a first drug - at least in the clinical studies - or run out of money[1].

[i] General remarks: To ease readability and reflect the legal framework of 2012, the sequence of "Study" and "trial" will be used synonymously as well as "drug" and "medicinal product".

With the explosion of the "dot.com" bubble in March 2000 the whole Biotech sector also fell by some 20%[2] after the former US President Clinton and the British Prime Minister Blair supported free access to research on the mapping of human genes.
The decline continued way off after September 11 and turned the dip into a prolonged bear market[3].

Since then the sector has not really recovered. Continuous unfavorable capital markets, ever increasing regulatory constraints, high failure rates[4] in the proof of concept and drug development costs that lately are rising to US$ 1,7 billion per new drug[5], are causing today's investors to be much more reluctant and risk avers.

Therefore it seems logical that the key factors for investments require appropriate planning and decision making to minimize or mitigate risks that are inherent to the biotech business cases[1].

A plan is needed for the process of decision-making, the assessment of risks and the analysis of target performance comparison. An effective risk management requires a proactive project management and business development to enable the company's development to stay one step ahead from competitors[6].

Case Setting - Storyline:

*The company FlexiMab, based in Germany was a university spin-off, founded in 1993. It went through several rounds of financing before going public in 1998. With some 50 employees it was a typical small biotech company.*

*FlexiMab developed a proprietary and patented monoclonal antibody platform known as TwinBite – "Twin" for the fact of binding two antigenic targets and the homophone "Bite" or "Byte" for its aggressive "Mode of Action" and the fact that the humanized part of the antibody was modeled in silico.*
*The first products of FlexiMab were two genetically engineered bispecific single-chain antibody constructs. Bite antibodies use a T cell mediated killing mechanism for their Mode of Action (MoA), as T cells are the most potent killer cells in the body. Their seek-and-destroy mechanism is essential for fighting viral diseases and controlling the growth of some tumors, as shown for patients with NHL, ovarian, and colorectal cancer. FlexiMab's first indication was in Acute Lymphoblastic Leukemia.*

*Dave Hal, a former Big Pharma celebrity and now a serial biotech entrepreneur has joined FlexiMab, as a CEO recently. In his last assignment however, he was unlucky to be*

*the CEO of Dyionix Inc., a US biotech company. Despite of his skill set and intuition the first and only product of the company failed in the Phase 2 development. Subsequently the company had to lay off 90% of its headcount.*

*Some weeks after the Dyionix disaster, the board of FexiMab had dismissed the company's CEO and took the opportunity to merge with Dyionix still headed by Dave Hal – whether these events were more than a mere coincidence is not known.*
*This was an excellent move and business decision as Fleximab suddenly had a new CEO, could slip into the existing corporate shell of Dyionix (with a NASDAQ listing), and had a much stronger cash position.*
*Last but not least, the FlexiMab Inc. subsidiary at the US East cost with 10 additional employees provided the chance for an US tailored drug development program and to deal with the FDA from its "home territory".*

# PROJECT & DRUG DEVELOPMENT

## PLANNING AND SUCCESS - IF YOU FAIL TO PLAN YOU PLAN TO FAIL

Case Setting – Storyline:

*In his first two weeks at FlexiMab Hal walked around and participated in meetings, just listening. He talked to his management team and also to many other functional area members and had finally a feeling for the "company spirit" and the people's mindset: It was too much science driven.*
*In addition, there were many hierarchy levels but only 60 employees after the merger and sometimes no clear reporting lines. Many meetings were held with many people involved who spent hours discussing issues not listed in an agenda (if there was one). However, all employees felt informed properly and took pride in being part of a great community.*
*Hal took a day in the home office to develop a draft for an organizational realignment of teams, reporting lines, communication, and meeting objectives.*
*He invited his management team to an offsite. He wanted his direct reports to agree to some of the factors he deemed to be important for success and he wanted to create awareness for the situation of a small biotech company.*
*Hal[7] intended to present his reorganization ideas to get the line managers' buy in. Clearly the team would develop all of it, but Hal would be cautious to bring his managers back to his point of view when they strayed off course.*

"Drug development, from a process point of view, is fairly well understood (…) and most drug development follows a standardized generic gate-controlled staged sequence"[8] (see p50, Figure 3).
But is it running so smoothly and can everything be planned given the fact that only one of 5,000 tested compounds makes "it to the market and only 30% of launched products ever achieve enough profits to pay back their development costs"[9]?

"If you fail to plan you plan to fail"[10]. As a "Golden Rule" both CEO and senior management team must instill a culture of planning and risk awareness in every employee's mindset.
Sticking to this rule is inevitably important. However, it is only a necessary but not a sufficient prerequisite for success. There is no "Laplace demon"[11] and nobody can take a look in a crystal ball to notice all the unknowns turning to unforeseen risks and influencing the development course of a drug (see chapter Risks & Risk Management , page 12 page et seq. for a more detailed discussion).
A thorough proper planning is not the whole story as not all unknowns can be foreseen. To be successful leaders must have a good intuition - and a lot of luck. They need to have gut instincts for what could happen - to manage also problems related to unknowns and uncertainty.
In many cases, the power of intuition might help more than the ratio to accomplish the leadership theorem "do the right things" in order to navigate through these uncertainties.
The founders of Hexal AG, a leading generic drug company, often did neither want to see detailed planning nor full-blown business plans for their decision-making. "It's not a product business, it's a people business"[12] they stated. Their style of leadership was "Management by walking around"[13] being informed by talking to people.
To ramp up a new business or to restructure a larger enterprise was sometimes a matter of a brief meeting in the cafeteria. They built up their company mainly relying on their intuition and sold their enterprise for some €6 billion to Novartis after only 10 years.

## THE ORGANIZATION

Size matters - Small but beautiful

The differences of larger pharmaceutical companies and biotechs in advancing a product through the clinical phases, to ultimately launching it and making exceptional revenues are fairly small.
Differences manifest in how drug development is conducted in the two company settings.

In biotech SMEs, the focus of project management is very much on getting the most out of the budget given its tight limits (finance, cash, time). Biotechs work according to the principle of the "minimum effort" that might be best described as the attainment of the specified result with the lowest possible spending of resources („Minimalprinzip"[14]). In contrast, larger enterprises tend to work according to the principle of maximum result, i.e. to generate the maximal return with a given budget. This is not trivial and may cause a "Big Pharma mindset" with regards to a given project.

On the other hand, there might be the "Biotech mindset" of "whatever it takes"[15] i.e. a strong identification with the drug being probably the unique candidate available for development. The product is prioritized and this project is of utmost importance, irrespective of the likelihood of success in the clinical phases or at the market.
In larger companies there is a self-limiting trend as the success of the whole portfolio is important and to a much lesser extend the fate of an individual project.
Also the executive management does not focus on the project but rather on the portfolio level. This can lead to significant risks and delays[8].
In small enterprises a failure in product development could lead to a discontinuation of development and might be detrimental for the whole company. This has a good side also. It creates a sense of urgency and employees might be more diligent as there is little room for failure[15]. In addition to the limited financial resources of biotech SMEs these facts cause a different perception of risks as compared to Big Pharma and probably a more proactive and formal approach towards decision-making and risk mitigation[8]. A comparison of "small versus big" is provided in Table 2, p52.

Organization & Teams

Fleximab after its merger is a still a small company with 60 employees, €2 Million in annual turnover (licensees, laboratory services) and would benefit from a number of incentives for SMEs that include among others:"

a) Administrative and procedural assistance from the SME Office;
b) Fee reductions for scientific advice, scientific services, inspections and the establishment of maximum residue limits for veterinary medicines;
c) Waiver of the MeDRA licensing fee when registring with EudraVigilance. This is only available for micro- or small enterprises and not for medium-sized enterprises;
d) Fee exemptions for certain administrative services of the Agency;
e) Deferral of the fee payable for an application for marketing authorisation or related inspection;
f) Conditional fee exemption where scientific advice is followed and a marketing authorisation application is not successful;
g) Assistance with translations of the product information documents submitted in the application for marketing authorization" [16]

Case Setting - Storyline:

*Most of the incentives apply with regard to a Marketing Authorization Application (MAA) and are not of greater interest for FlexiMab as the company is at least five years away from filing. However a)-c) are very attractive and an application for a SME status was envisioned. The criteria of "Micro, Small, Medium" are as follows:*

| **Enterprise Category** | **Headcount** | **Annual Turnover ( Mil)** | | **Balance Sheet (€ Mil)** |
|---|---|---|---|---|
| Medium | < 250 | ≤ € 50 | or | ≤ € 43 |
| Small | < 50 | ≤ € 10 | or | ≤ € 10 |
| Micro | < 10 | ≤ € 2 | or | ≤ € 2 |

*In general the SME criteria apply to FlexiMab and it would fulfill the "Small" enterprise requirement[16]. However, as pointed out in the case setting, it had previously acquired the US biotech Dyionix. Therefore it has to be assessed whether the company is an autonomous partner or a linked enterprise. The latter would be the case if it had more than 50% of the shareholders' or members' voting rights in another enterprise[16].*

*Dyionix is a wholly owned subsidiary of Fleximab as it holds 100% of Dyionix shares. Thus, Dyionix is a linked enterprise according to Art. 3.3 of the COMMISSION RECOMMENDATION of 6 May 2003[17]. In this case the US headcount and financial data have to be added to FlexiMab's corresponding numbers to calculate the threshold. Even after the addition of the US affiliate, Fleximab still meets the SME requirements for a "Small" enterprise.*

*The lessons learned for Feximab's management team are:*

1. *Listen to your intuition also and use it together with your ratio,*
2. *Understand that the "runway" for FlexiMab is rather short given its current burn rate and a clinical program ahead,*
3. *Keep your positive spirit and that of your teams,*
4. *Do not be blind for reality and do not fall in the "whatever it takes" attitude*

People make Projects - Projects Mean Teamwork

Drug development is a task that needs to be guided by a project management approach. It can be described as „the application of knowledge, skills, tools, and techniques to project activities to meet project requirements"[18].

Project management can only function with teams. "TEAM" in the sense of "Together Everyone Achieves More only works if all members within one and across all teams fulfill their tasks. All functions are equally relevant and mutual respect is as important as experience and know-how.

The Project Management Committee (PMC[ii]) as a team reflects the R&D organization of the company represented by the department heads. All functions for getting a project from "bench to bedside" are included: Research, Nonclinical Development, Process Development, Regulatory Affairs, Clinical Development, and Marketing.
The tasks of the PMC are both operationally and strategically. The team evaluates product ideas, approves the product strategy, supervises the project- and product planning, delegates tasks and responsibilities, and has various other functions (Table 4, p53).

Across the pharmaceutical and biotechnology industry, Core Teams are ubiqitous.[8] Core Team members represent functional departments such as CMC, Clinical and others. They should be experienced people but not supervisors or department heads, as some people behave differently when a supervisor is present[19].
The number of team members should be minimized to enhance team efficiency and unnecessary meetings should be avoided. If work streams or a meeting agenda require additional input, colleagues on an ad-hoc basis would be invited.

The Core Team is responsible for the planning and implementation of specific work streams and the budget planning within the context of the overall development plan. A specific work stream for Clinical would be the planning, conduct, analysis and documentation of clinical trials. Typical work streams for CMC would be process development and validation for manufacturing, manufacturing of Clinical Trial Material, and drug supply. The Core Team reviews and manages the critical path[20] for the respective work stream. Any changes to key work streams that potentially impact the critical path have to be reviewed by the PMC. In order to meet these objectives, the Core Team assembles different working groups for different activities and tasks.

A Project Manager heads the Core Team. The task of the Project Manager is to achieve the defined project objective by adhering to budget and time schedules while fully meeting the required performance scope and achieving the product requirements.
The Project Manager is responsible for all aspects of planning, while it is the responsibility of the Core Team and Working Groups to implement the plan.

[ii] No naming convention exists for this leadership team

Being the interface to the Executive Management by reporting to the PMC the Project Manager might be a leader or a "primus inter pares". In any case he or she should have strong people skills and exercise a leadership by persuasion, as normally no direct authority will be assigned to that role (Table 3, p53; Table 5, p54).

Case Setting - Storyline:

*Some years ago FlexiMab did not even have an orgchart. In a small company everybody is informed and there is no need for formal meetings with 10 scientists having lunch in the same room. In a growing organization the desire for comprehensive information can become a problem - leading to unnecessary meetings and discussions.*
*Now with 60 employees there is still no need for a complex organization and FlexMab's management team developed a small matrix with two therapy areas and the involvement of CMC, Nonclinical, Clinical, Safety, and Regulatory Affairs. Hal described the reporting lines and general responsibilities of the different stakeholders (*Figure 1*, and* Figure 2*, p49).*
*Hal proposed two colleagues from the CMC and RA departments to coordinate and lead the two Core Teams. The management team further agreed on a code of conduct for communication and meetings:*
*The Core Team meetings should also serve as a blueprint for other meetings. Meetings should be organized for a specific purpose[19]. All attendees should know the meeting's objective in advance. It would be initiated with an invitation, an agenda that ideally comes from the invitees, and the minutes of the previous meeting.*
*The Project manager should chair and act as a facilitator taking care that the meeting stays focused and different opinions have a hearing[19]. Who does what and by when would be captured as action items. The chair should give brief overview of the last meeting's minutes, and make a summary at the end.*

## PROJECT MANAGEMENT - A TYPICAL PROJECT

"Do the right thing" from the beginning is a key imperative for the development process. In this context, especially for SMEs, it is also key to "do things right" and thus the process flow should be granular and formalistic with gate controlled decisions (go/no-go decisions) for important milestones and feedback loops to review the decisions made.
A model of the product definition and development process (of FlexiMab) is presented in Figure 3, p50. Each phase reveals the milestone to be reached and the relevant results i.e. clinical achievements (e.g. Phase 1, 2 studies). Below is an example for a typical project that may illustrate the process framework and decision making also for other

development steps.

Every product or project is based on an idea, an improvement (for example a line extension) from which the requirements for the product and for product development can be derived. The input and requests for new products can come from own employees, business partners, investigators, and the market. The product idea is presented to the Core Team or a senior management team (e.g. PMC) for evaluation (if the idea relates to a company wide issue).

If the product idea is accepted, the product begins to take shape in the product feasibility phase. Here, under the supervision of the Line Heads and the Project Manager, the product requirements (e.g. draft SmPC) and technology are defined and documented, initial cost calculations are generated, and the results are presented to a senior management team for product feasibility acceptance.

Project Start

The project starts when a decision has been made that all relevant prerequisites, general conditions and circumstances have been covered and defined accordingly. Specifically, these are as follows:

- Project plan is approved
- Project tasks and structure defined
- Project working team(s) specified
- Resources allocated
- Information and reporting system clarified
- Risks identified and actions for risks defined

The project and its planning become part of the overall product development plan that is exemplified in detail as a template in Reference 19, p115-135. After the prerequisites have been met, the project kickoff meeting is held and moderated by the Project Manager. The objective of this meeting is to inform all involved (especially in the working groups) about the project, project plan and schedules.

Project Execution

A milestone identifies each development phase. It is reached when the results, schedules and requirements are met. Then the next (usually more cost-intensive) phase is started.

The requirements, tasks and results of each development phase are documented. The project documentation describes the progress and reflects all project activities. The project documentation serves as a means for preserving experience and know-how and will be used for regulatory proposes.

Project Completion

When the project reaches its final phase, preparations must be made for an orderly project completion. The Project Manager is responsible for the following tasks:

- End-of-project analysis
- Preserving the collected experience and data
- Evaluate effort and costs, schedules, and duration

The end-of-project analysis and preserving the collected experience and data is handled as part of the project review. The final report documents the results and the experiences. The Project Manager remains responsible for the project until it is phased out.

## STAGES IN DRUG DEVELOPMENT

Drug development is constituted by three main projects, i.e. CMC Development, Nonclinical Development, and Clinical development. A comprehensive set of guidelines for these projects and associated project plans can be found in reference 21. The regulatory development plan is primarily built on the clinical development plan.

### Development of Chemicals Manufacturing and Controls

Biologics (Directive 2001/83/EC – Annex I, 3.2.1.1) are inherently complex and small changes in manufacturing (e.g. pH, temperature, culture media) can have a great and/or unexpected impact. These fluctuations may lead to altered product characteristics und ultimately to a "new product". In fact it is often claimed that with biologics "the process is the product". This complexity is also reflected by a number of guidelines, which are relevant especially for Monoclonal Antibodies (mABs).[iii] A number of risks are attributed to their manufacturing, e.g. protein instability, virus contamination of host cells, aggregation of molecules, and immunogenicity. In fact FlexiMab's mABs are secreted in a non-native form and up to 40% dimers and aggregates are found.

### Preclinical studies

The objective of preclinical studies is to get an estimate for a safe starting dose of the drug for clinical trials. Most studies need to be done under good laboratory practice[22] and a number of guidelines concerning biotechnological proteins and mABs need to be followed.[iv]

[iii] EMEA/CHMP/BMWP/14327/2006,EMA/CHMP/BMWP/86289/2010, EMEA/CHMP/42832/05, EMEA/CHMP/BMWP/14327/2006, EMEA/CHMP/BWP/157653/2007

[iv] EMA/CHMP/BMWP/86289/2010, CHMP/437/04, EMEA/CHMP/BWP/157653/2007, EMA/CHMP/ICH/731268/1998, EMEA/CHMP/BMWP/14327/2006, EMEA/CHMP/BMWP/101695/2006, EMEA/CHMP/EWP/192217/2009

Phase 1 and Phase 2 Clinical Trials

Phase 1 trials initiate the evaluation of drugs in humans to assess the drug's safety, the determination of a safe dosage range, and the identification of side effects in order to better understand the drug's clinical pharmacology[22]. To start a Phase 1 trial sponsors must submit an IND or CTA application to the FDA or EU Competent Authorities (CAs). This application must include the results of the preclinical studies. Sometimes the Phase 1 studies provide an early indication for efficacy if studied in patients with the target disease. Drug doses usually start at very low levels, and trial participants are monitored carefully as the dose is escalated.

Phase 2 studies define the best regimen to be used in pivotal clinical trials. They are designed to create first efficacy data and help to further indentify the drug's safety. Conventionally, the initial step is usually a Phase 2a clinical trial that may include e.g. late stage cancer patients and that is focused on an initial efficacy evaluation or proof of concept.
As soon as the Phase 2 is finished, Phase 3 Clinical Trial Material should be available and CMC should take care that the program will continue without any time delay. During both Phase 1 and -2 clinical trials the toxicology and stability programs continue as well as the up-scaling of the manufacturing process[19,22].

Phase 3 Clinical Trials

Phase 3 clinical trials are designed to confirm efficacy and to continue to evaluate safety with a larger patient population. These studies provide fundamental evidence that the drug meets the legal requirements for marketing approval, which is needed to satisfy regulators. A phase 3 trial usually involves clinical centers globally and can last for several years. Phase 3 trials are ideally double blinded, randomized comparative trials and the FDA as well as the EMA require typically two Phase 3 clinical trials for approval.
If the Phase 3 clinical trials are successful, a BLA or NDA (US)/MAA (EU) need to be submitted to the FDA or EMA respectively. The medium review time is 322 days for the FDA and 366 days for the EMA (survey of 2012)[23]. The FDA may include an advisory committee review[22] (e.g. an Oncology Drug Advisory Committee, ODAC).
Before starting Phase 3 studies it needs to be decided whether to use commercial material or Clinical Trial Material for the study.[19] This is a dilemma as nobody wants to invest in an upscale of manufacturing if it is still unclear whether the drug succeeds in a Phase 3 setting. In contrast "if the commercial scale material varies from the Phase 3 material, a clinical bridging trial will be required by the agencies."[19]

Pre Launch phase

There are many other activities requiring actions and decisions that are not described in the process model presented in Figure 3, p50. Some are smaller steps but nonetheless important. From a regulatory perspective these Milestones encompass e.g.: Eligibility assessment for the Central Procedure, first CTA, IND, Scientific Advice, PIP-Interactions with the PDCO, EoP2 meeting, Accelerated Assessment procedure, Orphan Drug Designation(s), preparing a value dossier for Health Technology Assessment (HTA) agencies. Some of these important activities are summarized in Table 8, p56.

## RISKS & RISK MANAGEMENT IN PROJECT DEVELOPMENT

Projects imply risks. "Risk describes the likelihood that a chosen action or activity (including the choice of inaction) will lead to a loss (an undesirable outcome)"[24].

Risk Management

"Risk management is the systematic process of identifying, analyzing, and responding to project risk and develop strategies to reduce or avoid them"[25]. The goal is to improve project performance and leverage opportunities. Thus, risk management is a proactive, systematic and creative process that is constituted by the phases[6]: Risk management and risk identification, risk assessment, risk response planning, monitoring and control.

Risk Management Planning and Risk Identification

Even clear objectives and extensive planning may not prevent situations that require changes or deviations from plans: A business partner may request changes, coworkers may be unavailable, solutions may fail and schedules may fall apart. In the "planning phase the subject of risk management must be defined and scoped"[6]. Using checklists (with high level categories such as in Table 1, p51) or a team brainstorming may be helpful for that purpose. According to the Project Management Institute the objective of risk identification is to differentiate the issues that may have an influence on project results and to identify their characteristics with the objective "that those issues that have been anticipated in advance are easier to handle."

Risk Assessment

Using either qualitative or quantitative techniques, risks are further analyzed by assessing the risk's probability and its effect on project goals. Risks should be prioritised to judge the probability of project results more realistically.

Qualitative assessments of Risks:
An easy and intuitive approach to rate probabilities and impacts is to rank them as high, medium, and low[6] (compare pp37 et seq. for more details). Probability-impact matrices are a means to illustrate these probabilities and impact scales (Figure 4 and Figure 5, p51). A risk score could then be calculated as the "{probability of risk to occur} x the {impact on objectives}".
Risk impacts can sometimes be converted into financial impact terms to make risks also comparable across different projects. "When risk impact and probability is known, the decision with greatest value can be assessed" [25].

Quantitative Assessments of Risks:
A number of other techniques are used for the assessment of risks, such as Poisson-, Exponential-, Normal-, and Beta-distribution. "Current leading edge theory and practice in quantitative analysis includes risk option weighting and efficient risk horizon modeling."[27]
Monte Carlo simulations are also often utilized[6]. In the qualitative probability-impact matrices described above each uncertain variable within a model is assigned a value such as low, medium, high and then the results are recorded. A similar approach is used in Monte Carlo simulation but all variables are modeled with value ranges (low=1, medium=2 high=3) and probability distributions (i.e. anything between 0-100%). In addition numerous iterations are performed with variables ranging randomly within their probability distributions. As a result e.g. the total project cost and time could be obtained as the probability function (compare p34 and Figure 6 Monte Carlo Analysis of eDMS/eCTD Project for a more detailed example).

Risk Response Planning and Monitoring & Control

The objective of risk response planning is to decide how to reduce the indentified risks and/or to increase the project's opportunities. Responsibilities have to be assigned to a risk owner and need to be monitored on a regular basis.
Together with the Core Team, the Project Manager has the important tasks of recognizing risks, identifying and evaluating project-relevant risks, and making decisions.

The monitoring and control provide answers "whether the project assumptions are still valid" [25], contingency plans should be implemented, a project should be preplanned, and risk "responses have been implemented as planned".[25]

A risk should be taken when the costs to eliminate the risk are larger than the possible costs imposed by the risk. There are generic response strategies that include to "mitigate, prevent, transfer, insure" risks and the minimum option would be to at least accept a risk (see Table 7[26], p55).

## RISKS AND RISK MANAGEMENT IN DRUG DEVELOPMENT

Drug development is a risky business, and some of these risks are summarized in Table 1, p51.[6,27]

As compared to Big Pharma, SMEs are affected more severely by the consequences of failures. SMEs can at best afford only a few concurrent development projects and if they have to bet on one horse the risk of failure is considerably bigger as compared to large pharmaceutical enterprises.

Provided there is a platform technology (for example, antibodies can be adapted to multiple targets) it might be possible to do research for more than one indication[6]. However, toxicological and clinical studies have a very high risk of unfavorable outcomes as of 5,000 screened compounds no more than 250 move to preclinical phase and of these only 5 enter clinical testing[9]. Thus, it is important to eliminate all projects with poor prospects early, as clinical studies account for approximately 40% of total R&D costs[28].

Product safety is a crucial element of the overall management of uncertainty - especially in the life sciences sector.[29]

A drug candidate is assessed by the fundamentals of "Quality, Safety, and Efficacy". The requirement of quality may never be compromised. ICH Q9 had focused on the concept of „Quality Risk Management[30] and „quality aspects should not, in themselves, be a source of risk"[31]. In contrast, there is some different notion regarding safety and efficacy. These two conditions may not be seen separately and are interdependent in reality. Frequently a higher efficacy leads to increased adverse events and vice versa[v]. This phenomenon is described by the concept of the risk-benefit ratio.

A medicinal product only receives Marketing Authorization when the risk-benefit ratio is proven at the time the medicinal product is authorized. However, it is a known fact that - not only in rare diseases and conditional[36] marketing authorizations - there is a limited safety base available to identify the drug's safety risks in a comprehensive way. Thus,

[v] Today's concept of therapy may be described as the predominant "one size fits all". There is still neither hardly a personalized approach nor many tailored drugs. These would probably shift the risk-benefit ratio towards higher efficacy while a base level of adverse events remains.

some of these risks are identified only years post launch.
The judgment of risks and consequently the assessments of the risk-benefit ratio is the recurring theme throughout the entire life cycle of a drug.
So, within the development phases this theme is accomplished within e.g. the DSUR[32], the investigator's brochure[33], in clinical trial applications[34], in the informed consent[35], and also within full or conditional[36] Marketing Authorizations. The ratio is also crucial, when it comes to renewals[37]. In addition the EMA may "at any time ask the holder of the marketing authorization to forward data justifying that the risk-benefit ratio is still favourable"[36].

Preclinical & Clinical Risks With Engineered Antibodies

As a result of the tragic TGN1412 case, the EU guideline "Strategies to identify and mitigate risks for first-in-man human clinical trials with investigational medicinal products"[38] has been released. The guideline addresses the identification of the special risk factors attributed to mABs that derive "from particular knowledge or lack thereof regarding (1) the Mode of Action, (2) the nature of the target, and/or (3) the relevance of animal models"[38]. The PEI regards mABs as a new type of engineered structural format or fusion protein and therefore as a potential risk factor[39].
Animal models should be as close as possible to the human disease and it would be regarded as a risk

"if animal species/models or surrogates are perceived to be of questionable relevance for thorough investigation of the pharmacological and toxicological effects of the medicinal product" (…) "The ability of non-clinical studies to predict safety issues in humans may be limited because the nature of the target is more specific to humans or because of other factors".[36]

A novel mechanism of action might not necessarily be a risk in itself, but the novelty and associated level of knowledge should be reflected[36].

Many mAb products are known to be associated with unwanted immunogenicity such as loss or reduction of efficacy, local reactions, major allergic reactions, which may impair clinical response. The "Guideline on immunogenicity assessment of monoclonal antibodies for in vivo clinical use"[40] that came into effect in Dec 2012 considers these risks. This guidance should be adapted for each mAb development program. These programs should be based on the identification of risk factors inherent to the particular mAb, the final drug product and the treated patient population.

Case Setting - Storyline:

*The first products of FlexiMab were two Bites, genetically engineered bispecific single-chain antibody constructs of murine origin. Bites are bispecific as they combine two targets in a single antibody:*
*One end of the antibody molecule holds a target for CD3, which is able to bind to T-cells; the other end of the Bite contains either a target for EpCAM (TwinBite9) or a target for CD19 (TwinBite7). CD19 and EpCAM are expressed on different tumor cells.*
*Bites binding to both T-cells and tumor cells can elicit the subsequent killing of tumor cells. Due to the abundance of CD19 in B-cell malignancies (TwinBite7) or EpCAM (TwinBite9) in epithelial tumors Bites can address a range of hematologic or solid tumors. As such, FlexiMab regards Bites not only as products but also as a platform for a pipeline of products.*

*In 2002 FlexiMab conducted three Phase 1 dose-escalation studies in the EU, in which TwinBite7 was administered as a short-term infusion (2 hours) to a total of 30 patients with relapsed or refractory NHL. All three studies were terminated early due to the occurrence of CNS events, or infections.*
*This was a major drawback for the development program but the idea came up to alter the short-term infusion from 4h to a continuous infusion of 48h (using a pump) to mitigate the observed adverse reactions.*
*One year later*[vi] *FlexiMab was ready for another trial and conducted an open-label, multi-center, dose escalation Phase 1 study – FlexiP1. It was designed to investigate the safety and tolerability of a continuous infusion of TwinBite7 in 80 patients with relapsed NHL over four to eight weeks. The patients were enrolled into dose cohorts (0.5 µg/m²/day up to 90 µg/m²/day). The latter dose exceeded the maximum tolerated dose (MTD). The clinically most relevant adverse events were again CNS events, which were fully reversible. However, at a dose of 15 µg/m²/day, anti-tumor activity in bone marrow and a favorable safety profile was shown.*
*Hal wanted to learn about potential consequences for the Bite antibody development program from the company's Clinical Department in light of the TeGenero case and the relevant guidelines. In addition the Nonclinics department should take care of the "Immunogenicity assessment of monoclonal antibodies", which - in contrast to a guideline of 2006 addressing biotechnology-derived therapeutic proteins*[41] *- also reflects on novel mABs. These novel mABs include e.g. Fab fragments, scfv, nanobodies, and minibodies.*

[vi] In contrast to the short term infusion, the continuous infusion required a portable pump. The administration of the drug was much more complex and the setup took time for development

*The teams came back with the following results:*
*In fact TwinBite7 was likely to bear a higher risk than other mAB approaches.*
*First of all the Bite employs a new Mode of Action. However, the Bites´ MoA is directly intervening with the natural immune response and negative effects such as inflammation, infections, and immunogenicity cannot be ruled out.*
*Secondly, Bites address targets for which no appropriate animal models exist. Thirdly, being a recombinant fusion protein (assembled by two scFv fragments), the antibody has a completely new type of engineered bispecific format (natural antibodies are directed only against one antigenic determinant).*
*Furthermore, TwinBite7 is humanized only in some sequences and for the greater part is of murine origin. It was administered repeatedly for quite a long time, i.e. for two weeks per cycle.*
*All these factors might contribute to a potential risk of immunogenicity that should be assessed.*
*The team had already evaluated all patient sera from the FlexiP1 trial and notably only in 1 of 80 patients immunogenicity was detected. Administration of low doses by continuous infusion and the highly effective depletion of normal B cells may favorably contribute to the low immunogenicity of TwinBite7 in patients. To avoid the risk of false negatives due to a low sensitivity limit of the assay, the team had switched from a bridging Elisa with chemical amplification to a more sensitive electro-chemo-luminescent assay (see guideline).*

*The only relevant species would be chimpanzee but for ethical reasons these monkeys cannot support a nonclinical development program.*
*Therefore Tus107, a murine surrogate molecule was constructed and used in the main non-clinical studies. The concept of TuS107 was agreed by some CAs, namely FDA, PEI, and MHRA. Remaining risks might still be attributed to the question, why no transgenic animal was engineered or EMA could argue that TuS107 is still not relevant. However, the teams regarded these risks as low.*

Managing Drug Safety Risks

In many countries, risk management plans (RMPs) are required and submitted to Health Authorities with an application for a new marketing authorization[43].
The RMP's objective is to identify what is known and not known about the safety of a drug at the time of submission (Safety Specification) but also to further characterize its safety risks post approval (Pharmacovigilance Plan). In addition the RMP needs to "define appropriate measures to minimize known risks to patients and to monitor the success of those measures (Risk Minimization Plan and Evaluation of Effectiveness)"[43].

In the ICH regions the Tripartite Guideline Pharmacovigilance Planning—E2E (2004) provides part of the regulatory framework. In 2005 the EMA published the "Guideline on Risk Management Systems for Medicinal Products for Human Use" while the FDA issued the "Guidance for Industry Format and Content for Risk Evaluation and Mitigation Strategies (REMS)" in context with the FDA Amendments Act of 2007.
As part of a new pharmacovigilance legislation in the EU, addressed by Regulation (EU) No 1235/2010 and Directive 2010/84/EU (amending Regulation (EC) No 726/2004 and Directive 2001/83/EC) the "Guideline on good pharmacovigilance practices (GVP)" covering RMPs was made available (July 2012).
The "Module V – Risk management systems"[42] replaced the corresponding chapter of Volume 9A. It reflects on "how to maximise, or indeed assess, the risk-benefit balance". In this context "risks need to be understood in the context of benefit[42].
The RMP is a dynamic, stand-alone document and its purpose is to indentify risks and to allow for risk minimization or mitigation whenever possible.
A RMP should not only be submitted with a new application, renewal, or a significant change to an existing license but also "at the request of the Agency or national competent authority when there is a concern about a risk affecting the risk-benefit balance"[42]. Thus, RMPS are relevant at any point in a drug's lifecycle from pre- to post-authorization phases.

Case Setting - Storyline:

*Since the First in Man studies it was evident, that under TwinBite7 therapy patients may experience a spectrum of CNS events such as encephalopathy, including confusional and cognitive disorders, convulsions, and speech disorders. Most of these Adverse Events were reversible after dose reduction or treatment termination.*
*However, in the FlexiP1 study, a patient with a history of a HSV-reactivation and a Graft versus Host Disease after prior stem cell transplantation experienced a fatal Serious Adverse Event (SAE). This SAE, an invasive fungal infection, occurred after the patient experienced psychosis and other neurological symptoms. The patient's general condition during treatment worsened and therapy was discontinued. Nevertheless, the patient died a few days after treatment stop and an autopsy report revealed fungal encephalitis and brain stem infarction due to a fungal thrombus as cause of death. Both investigator and FlexiMab assessed the event as serious, unexpected, and possibly related to the study drug. The SUSAR was processed as an expedited reporting inline with Directive 2001/20/EC, the GCP Guideline and other local applicable guidance (Germany).*
*However, this case differed from the usual neurological adverse events seen in some patients treated with TwinBite7, as along with neurological signs it revealed multiple seizures, a HSV re-activation and a low HSV positivity in brain biopsy.*

*The company regarded this case as an urgent safety issue and took additional action in accordance with EU Directive 2001/20/EC, Detailed Guidance 2010/C82/01 and Detailed Guidance ENTR/CT 2. Such urgent safety measures need be taken if an event relating to the conduct of a clinical trial is likely to affect the safety or health of trial subjects.*
*It can be implemented without prior approval from applicable Competent Authorities and Independent Ethics Committees, but these bodies must be notified ex-post as soon as possible after safety measures were decided or taken.*
*Actions were coordinated by FlexiMab's Safety Working Team and Company Safety Committee - two cross functional teams assessing the safety of clinical trial subjects and giving strategic input on drug safety issues, respectively.*
*The teams decided against a discontinuation or temporary hold of the clinical trial. Rather they recommended (to the executive Management and subsequently to the CAs) a text amendment to the IB and protocols including the wording "urgent safety measure"that should be initially communicated via a "Dear Doctor Letter".*
*Hal agreed but was not satisfied. He requested from the Safety Working Team and Company Safety Committee to start working on RMPs for both TwinBite7 and TwinBite9.*
*He disagreed that a RMP would be handled as a pre-authorization issue to be addressed later in development, as there was plenty of time to approval. He also did not accept the notion that there are many other relevant things to be done in an urgent manner.*
*Hal argued that some years ago safety was divided into a pre- and a post-marketing phase but now Health Authorities regarded it as a "Life Cycle" discipline. Prevention would now be in focus and not only passive observation.*
*Finally he challenged his team to collect the arguments for a RMP at this stage of development. After a brain storming session, the team delivered the following list in favor of a proactive RMP approach:*

- *"No/fewer delays of approval due to safety issues (fewer safety questions by Health Authorities during approval review and shorter time required to answer those questions)*
- *Better control of which safety risk management activities are required if risk identified internally and risk management activities proposed by MAH rather than mandated by Health Authorities*
- *Decreased risk of marketing restrictions, unfavorable label changes and product withdrawals from market*
- *Improved reputation and trust with Health Authorities and public resulting from proactive, responsible, and transparent handling of safety issues*
- *Internal consistency around communication and knowledge of safety information of projects/products."*[43]

*These are the lessons learned for Feximab's management team:*

- *"Know What You Know" [29:] Drug safety knowledge must be integrated into the entire life cycle management of the drug, from early discovery until the end of commercialization.*
- *"Know What You Do Not Know"[29]: It is key to understand which gaps exist in understanding the drug's safety. These must be identified as early as possible, and the company should discover these potential safety risk prior to a regulatory agency.*
- *"Have a Plan"[29]: A company with no acceptable RMP at time of approval may at best receive a limited SmPC, accept approval delays or jeopardize approval as a whole.*

Case Setting – Storyline:

*Only six months after the positive (intermediate) outcome of the Phase 1 dose-escalation trial, the company initiated a "Proof of Concept" study, FlexiP2 as an open-label, multicenter, Phase 2 study (conducted in the EU). Efficacy, safety, and tolerability of TwinBite7 in adult patients with Minimal Residual Disease (MRD) following standard first line therapy in ALL were investigated.*
*MRD is defined "as small numbers of leukemic cells that remain in the patient during treatment, or after treatment when the patient is in remission showing no symptoms or signs of disease"[44] and MRD could be regarded as a prognostic marker with clinical significance.*
*After one year, 20 patients of FlexiP2 were evaluable for the efficacy analysis. A complete MRD response (MRD negativity, i.e. one cancer cell in 100,000 healthy cells) was observed in 16 out of 20 evaluable patients, i.e. with response rate of 80%. This was an unexpected success.*
*In parallel to the ongoing Phase 2 study, Hal felt it was time for the next move. He wanted to conduct a clinical program in the US, ideally in ALL as an orphan indication and MRD as a biomarker in both adults and children. He requested to prepare an "Orphan Drug Designation" (ODD) application for TwinBite7 in ALL as a search in the EMA and FDA databases had revealed 16 ODDs and four approvals for ALL (i.e. „lymphocytic or lymphoblastic leukemia") [45,46,vii]. None of these products had a similar MoA as compared to TwinBite7 and it was clear from estimations that there was enough market potential for another ALL drug.*
*He organized an offsite with his management team to discuss how to proceed strategically and tactically with the findings from the MRD ALL study FlexiP2:*

[vii] Figures are based on year 2007 - the year before FlexiMab was granted the ODD.

- *What are the options to advance this indication as fast as possible in the US but also in the EU? Where are the differences?*
- *What kind of trials would be needed for an Accelerated Approval?*
- *What are risks attributed to an Accelerated- or Conditional Approval?*
- *Could Minimal Residual Disease be regarded as a valid biomarker?*
- *What would be the regulatory strategy to follow?*

## ACCELERATING AND FACILITATING REVIEW AND APPROVAL OF NCES

Orphan Drugs

Between 5,000 and 8,000 distinct rare diseases are known today, affecting between 6% and 8% of the population in total[47].
Rare diseases are life-threatening or chronically debilitating conditions (in the US the term serious is used) affecting no more than 5 in 10,000 people in the EU (i.e. 253,000 people in the 27 EU member states) and fewer than 200,000 people in the US.

About one fifth of the orphan drugs approved are biologics and roughly 35% of these are oncology drugs[48]. Orphans have a shorter FDA review time on average (1.6 years) than other NCEs (2.2 years).[49]
The Orphan Drug legislation provides several incentives for the drug development including a seven (US) or 10 years market exclusivity (EU), tax credits, and waivers or reduced fees for approval in the US or EU[49].

For drugs that address unmet medical needs and for serious or life-threatening conditions, both FDA and EMA have implemented a variety of options and procedures for expedited assessment and approval. These include fast track status and review / rolling submission (US), accelerated assessment (EU), accelerated approval (US) and conditional or exceptional approval (EU). These options seem to be used more frequently for orphan drug applications than for other applications [50].

FDA's accelerated approval (AA) allows the use of surrogate endpoints that are "reasonably likely to predict clinical benefit"[51]. The use of surrogate endpoints is also feasible in the EU and was defined in the context of the "Guideline on clinical trials in small populations"[52]. The FDA used the AA process to approve 90 drugs based on surrogate endpoints between 1992 and 2008.[53] Both agencies require post-approval studies to develop further evidence about benefits and risks based on clinical outcomes.
Another mechanism to facilitate review and reduce regulatory uncertainty and risk is the Special Protocol Assessment (SPA). It allows the FDA to provide expedited review to

clinical trial protocols and to reach a mutual agreement between sponsor and agency on the design and size of trials[54].

Still the FDA was criticized of being too slow in granting approvals. Thus, three new bills were introduced to the US legislative coordination process 2012, namely the FAST and TREAT[55] bills - amending accelerated approval - and a bill concerning a "breakthrough designation" for drugs that "demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints"[56]. These drugs would "typically have a compelling scientific rationale and promising mechanism of action, such as targeting a molecular driver of a biologically characterized disease"[57]. The FDA would hold meetings with the sponsor, provide timely advice, facilitate an efficient review, and involve senior managers to "ensure that the design of the clinical trials is as efficient as practicable"[58].
A comprehensive assessment of the US expedited approvals is provided in Table 10[59] and in Table 11[57] p60 and a comparison of the parallels and differences US versus EU is presented in Table 9, p57.

Accelerated Approval

The Oncologic Drugs Advisory Committee (ODAC) is a powerful panel of experts. The ODAC makes non-binding recommendations to the FDA whether to approve an oncologic drug, but also regarding processes that are of interest to the agency. In many cases the FDA follows the committee's proposals.
In 2009 and 2011[60] the FDA had asked the ODAC to hold a meeting reflecting the AA process and to review why some sponsors had missed their deadline to fulfill their post-marketing confirmatory study commitments. The overall goal was to see whether the expedited program for cancer drugs could be optimized.
The FDA claims that AA is successful as 37 cancer drugs (in 49 indications) have been approved and only five have failed in confirmatory trials.
Most companies seeking FDA approval must provide data from two well-designed Randomized Controlled Trials (RCTs). The agency's oncology office, however, has frequently granted AA on the basis of data from a Single Arm Trial (SAT) measuring a surrogate endpoint that is "reasonably likely" to predict clinical benefit.
By granting AA based on surrogate endpoints, the FDA expects a small percentage of drugs to fail in confirming clinical benefit. This could be regarded as a trade-off for early availability of promising drugs for severe and life-threatening diseases. However, it highlights the importance of due diligence and early integration of post-marketing trial design into a comprehensive drug development program (see below).

Randomized Controlled Trials - Standard in Accelerate Approvals

SATs are not a sufficient basis for AA. However, they can be useful in oncology as part of an overall drug-development program in rare patient populations and with drugs that show exceptional efficacy.
On the few occasions where SATs might be acceptable, they should include a robust primary endpoint and, ideally, have historical baseline information to compare against.
If the ODAC succeeds to convince the FDA, sponsors that receive AA will need to conduct at least two adequate and well-controlled trials to confirm the clinical benefit of their drugs[61].
The panel argued that RCTs are possible most of the time. In fact, out of 49 trials that were the basis for accelerated approvals, 20 were initially randomized and comparative and 29 were SATs.[61]
SATs may be the only option for trials enrolling patients who have not responded to all other therapies. However, the ODAC argues that even then a RCT with an active comparator could be run in a less refractory population or as a comparison against best supportive care. Thus, in the view of the ODAC in many cases a RCT seems to be feasible from the beginning.

Confirmatory trials must be under way early

The median time to verify and describe the clinical benefit in post-marketing trials is approximately four years but can be up to over 12 years[61]. One third of accelerated approvals exceed 6 years to fulfill post-marketing commitments.
These long timelines would not be problematic if all confirmatory trials would demonstrate a clinical benefit at the end (which is not the case). Consequently, post-marketing trials should confirm (or fail to confirm) clinical benefit as early as possible. This should decrease the level of uncertainty associated with an AA and lead to prompt withdrawals of approvals for drugs having failed[61].
As a consequence the ODAC recommends that at least two RCTs need to be under way (i.e. enrolling patients) prior to granting AA. Without these ongoing trials, a package for AA would not be allowed to file.[61] In cases where the AA was granted with a SAT, at least the confirmatory trials should be RCTs.

Risks Associated With Accelerated Approvals

Not all AAs are converted to regular approvals with confirmed clinical benefit. Almost 45%[61] of all drugs remain on the market with a potentially unfavorable risk-benefit ratio. In other words AA is a risk for both FDA and MAH. There is no regulatory definition for "due diligence" related to conduct and completion of post-marketing clinical trials and therefore no particular guidance for the AA holder. FDA considers it not to be acceptable to market a drug with at a potentially high level of toxicity for many years.

As a consequence Title 21 Sec. 601.43 provides withdrawal procedures for AAs under the following conditions:

"(a) For biological products approved under Secs. 601.40 and 601.42, FDA may withdraw approval, following a hearing as provided in part 15 of this chapter, as modified by this section, if:

(1) A postmarketing clinical study fails to verify clinical benefit;
(2) The applicant fails to perform the required postmarketing study with due diligence;
(3) Use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the biological product;
(4) The applicant fails to adhere to the postmarketing restrictions agreed upon"…[62]

In addition, a failure in meeting Phase 4 commitments may result in civil penalties ranging from US$250,000 per violation up to US$1 million. If violations continue after prior notice, FDA may impose penalties up to US$10 million.[63] However, these penalties seem to be unused as a "regulatory stick" as the FDA so far has not imposed such fines.

For a company holding a MA based on a Conditional Approval in the EU, the risk is even more substantial. Although no such penalty system exists in the EU, the approval is subject to specific obligations (post approval commitments) also and to a renewal every year[64].

Running a SAT hoping that a compound would show an exceptional response rate would be a gamble and the sponsor could be better off to "choose" the RCT option right away.

Given all these discussions and potential problems, the drug developer should follow an appropriate risk mitigation strategy e.g. to ask for early scientific advice, discuss confirmatory study protocols in EoP2 meetings and achieve agreements under Special Protocol Assessments (SPAs).

## SURROGATE ENDPOINTS IN CLINICAL TRIALS

A surrogate endpoint has been defined as a biomarker "intended to substitute for a clinical endpoint", the latter being a characteristic or variable that reflects how a patient feels (quality of life), functions (morbidity), or survives (mortality).[65] It "is expected to predict clinical benefit, harm, or lack of benefit or harm"[66].
In oncology a valid endpoint would be overall survival. However, as such studies often run for years, cancer drugs are currently approved mostly on the basis of surrogate endpoints, such as time to relapse, time to disease progression, progression-free survival, or hematologic response. "Surrogate endpoints for accelerated approval must be reasonably likely to predict clinical benefit (21 CFR part 314, subpart H and 21 CFR part 601, subpart E). In addition, drugs also must provide a benefit over available therapy."[67] The following endpoints in cancer trials were acknowledged by the FDA (Table 6, p54) as surrogates: "Disease-Free Survival, Complete Response, Progression-Free Survival (includes all deaths) or Time to Progression (deaths before progression censored), and Complete Response."[61]
According to the EU "Guideline on the evaluation of anticancer medicinal products in man" (CHMP/EWP/205/95) the preferred endpoint to prove efficacy for mABs in cancer indications would be either Progression Free/Disease Free Survival or Overall Survival.

Surrogate endpoints may be considered validated if they are

"sensible, measurable, interpretable and highly accurate in predicting the clinically relevant endpoint. A surrogate endpoint is correlated to the final clinical endpoint if it fully captures the net effect of intervention on all mechanisms that influence the clinical outcome and reflect the totality of the effect" [68].

In addition, the intervention on the surrogate endpoint must predict the effect on the clinical endpoint.[69] Health Technology Assessment agencies such as the IQWIG request biological plausibility (e.g. causal pathway, animal models) and empirical evidence (e.g. results from RCTs) as criteria to accept an endpoint supporting (clinical) effectiveness.[88]

Minimal Residual Disease - a Valid Biomarker

ALL is a rare malignant disease (incidence rate: 1.6 in 100,000 per year) with a poor prognosis and a very high medical need. About 60-70% of adults and 15-20% of children die from treatment-resistant or recurrent ALL and/or from short- or long-term adverse events of therapy.
Although achieving first remission is a success, relapses cause long-term mortality of 60-70% in adults and 10-20% in children. Very early relapse carries a markedly poorer prognosis than late relapse. Minimal residual disease (MRD) positivity is the major cause of relapse in leukemia. MRD levels <0.01% (i.e. less than 1:10,000 leukemia cells) can

be assessed by a sophisticated "Polymerase Chain Reaction" (PCR) within the first three weeks of therapy. High MRD levels are associated with a three year relapse rate of >90% while the relapse rate in patients with a persisting MRD level of <1:10,000[70] is 0%. Thus, the MRD levels can be regarded as a surrogate marker with clinical significance.

Case Setting – Storyline:

*In an EoP2 meeting held later the FDA made the following statement:*

*"MRD has not been used by FDA as a surrogate endpoint likely to predict clinical benefit in support of accelerated approval nor as a measure of direct clinical benefit. A validated surrogate endpoint requires demonstration in a randomized trial that an effect of an intervention on the surrogate endpoint reliably predicts the effect of the intervention on the clinical outcome. Even when there is a well established causal pathway for the marker's effect on the endpoint, the marker may not function as a reliable surrogate endpoint."*

*In addition FDA stated that MRD was a prognostic biomarker (related to disease outcome) and not a predictive biomarker (related to treatment outcome).*
*This was rather striking for Fleximab as a few weeks later, a search in ClinicalTrial.gov database[71] revealed that Genzyme had initiated a study with FlexiMabs's competitor product, Clofarabin using MRD as the primary endpoint in ALL.*
*In a Scientific Advice meeting the EMA took a different view and agreed to the use of MRD as a surrogate endpoint but requested further validation.*
*FlexiMab agreed that a thorough assessment of the validity of the PCR methodology is imperative from a regulatory perspective.*
*Therefore, the company audited the PCR laboratory of this study. During this audit it became apparent that the laboratory site has already employed high quality standards. Numerous validation studies (including European ring tests for some key parameters of the PCR method) had already been conducted and also partly been published. A limited number of missing validations had been identified.*

## REGULATORY STRATEGY OF FLEXIMAB

*MAAs are envisioned in the USA and all European countries. In both regions 2 eCTDs will be filed that differ mainly in Module 1 with minor variations in module 3 due to some US peculiarities.*
*In both regions the regulatory strategy is based on the approval for ALL around 3 development lines. It is intended to address indications with high unmet need to ultimately establish TwinBite7 as a key component in ALL treatment. The first line is in adult patients with relapsed/refractory ALL. The second line is in adult patients with MRD positive ALL, a high-risk front line setting. The third line is in pediatric patients with relapsed/refractory ALL.*

*Regulatory Strategy for line 1: The initial indication planned for filing in both the US and EU is in adult relapsed/refractory ALL and the key focus is to support accelerated and conditional approval.*

*This strategy is based on three trials including a dose-exploratory Phase 2 study, a single-arm Phase 2 study, and a RCT. FlexiMab has received written advice in the context of a Type C meeting request. The FDA responses were overall positive and consistent with the program as proposed.*

*Regulatory Strategy for line 2: The second ALL development track is in front-line/consolidation adult ALL. For US approval in the first line adult ALL setting, a Phase 3 RCT is required.*

*The ongoing Study FlexiP2 (MRD-positive ALL) by itself would not be sufficient for an US label as the FDA currently does not consider complete molecular response being a validated surrogate endpoint predictive of clinical benefit (see above). Thus, the regulatory strategy to achieve a first-line/consolidation label in the US also includes at least one Phase 3 RCT.*

*In the EU a pre-requisite for filing in this indication based on the single arm study FlexiP2 would be that the patient population is considered to have an unmet medical need, and that the outcome of study FlexiP2 is considered exceptional in relation to historical data. In this context, FlexiMab intends to consolidate an adequate historical database matching the study population in order to substantiate the trial data. In addition, the medical need of this patient population will be evaluated in a literature review*[viii]*.*

*Regulatory Strategy for line 3: The initial pediatric program and a Phase 1/2 pediatric clinical in relapsed/refractory ALL trial have been discussed with FDA at an EoP2 Meeting. In addition, a revised European PIP will be filed to the EMA's pediatric committee (PDCO) based on study design adjustments after discussions with FDA. Depending on the outcome of the study, discussions with regulatory health authorities are planned and faster registration pathways may be considered.*

[viii] W. Meyer, personal communication

## BUSINESS DEVELOPMENT

Business development is not clearly defined and a considerable overlap to project management exists. However, there is a number of tasks attributed to it both during the prelaunch phase but also post approval. These tasks may comprise: Establishing and maintaining a customer network, structuring of term sheets, negotiation of deals, evaluating and addressing potential partners for in- and out-licensing of intellectual property or technology, commercialization of products and technologies, contributing to the setup of corporate strategies, communicating the strategy to external stakeholders and potential partners[72].

## VALUE STORY & COMMUNICATION

Business Development is responsible to communicate a constant value story based on the company's value proposition to the "outer world", i.e. namely potential partners/buyers, investigators/physicians, patients, payers and decision makers (health care insurances, health technology assessment agencies). The value story should be in line with all "official" data (publications, studies etc.) but targeted to these different audiences.

Payers e.g. will not only take a look at the value dossier that the company needs to file in many countries. These bodies will also check what is to be found in the public domain. The information provided here must be the company's individual story otherwise the payers might build their own addressing potential concerns.

## CORPORATE SETUP & MODEL - A BUSINESS DEVELOPMENT TASK

As described below, business models in the pharmaceutical arena have been evolving constantly, as firms must recoup the highest value to recover their development costs. SMEs must be more flexible and creative regarding their business models to gain the greatest return from their innovations: Some offer research and services, "some produce tools, and others produce therapeutic products".[73]

The so-called "Fully Integrated Companies" are the leading drug companies that address all elements of the pharmaceutical value chain, i.e. they produce, develop, manufacture and market therapeutics (and sometimes diagnostics also).

However, these companies increasingly license or acquire innovations from biotechnology companies.

"The core competency of Big Pharma is size"[73], which is the ability to utilize considerably cash, economies of scale and a global organization to reach markets efficiently (compare p4 "Size Matters").
Only a few biotechs have made this jump and now play in the league of fully vertically integrated biotech companies. These are Big Biotechs such as Amgen, Genzyme (now Sanofi), and Genetech (belongs to Roche again).
When it comes to partnering, both small and big companies are in a dilemma. Big Pharma wants to fuel pipelines without risking too many resources, e.g. financials and own R&D capabilities. They have the spoilt for choice with dozens of SMEs wanting to partner or out licensing their technology.
From the SME perspective the choice is easier as there are only some 20 Big Pharma companies. However, the objective to partner is equally hard to achieve as multiple small enterprises compete for these few targets.
Some Big Biotechs, often now have platforms and products that originally did not "fit" to the typical mainstream portfolio of pharmaceutical companies. During the last decades of the past century, Big Pharma was slow to recognize the particular value of therapeutic proteins, "the field was left open for new companies that were able to do so." These Big Biotechs (see above) "defined commercial biotechnology" (….) [and] provided value to the industry not only as product innovators but also as process innovators"[73]. Today while "specialty drugs are prescribed for only one in every 100 commercial health plan enrollees, these drugs account for (….) [more than 15%] of commercial prescription drug spending in the US today"[74].

Biotech without own Research:

A means to mitigate risks for SMEs would be to limit drug development to post research building blocks of its value chain, to avoid cost intensive proprietary research. Such companies would focus on development while they "hope that by in-licensing innovations or acquiring companies, they will eventually build a deep and continuous pipeline."[75]. This model – although not innovative at first sight - is used by some companies and is a sucessful approach. Examples are Jerini with Icatitbant (purchased from Hoechst/Aventis), Vestar/NeXtar/Gilead with HIV compounds bought from a Czeck university, or Pharmion/Cellgene with Talidomid.

Biotechs with Platform Models:

Platform companies produce research, tools, or services creating value by licensing early-stage products to more advanced companies, which in turn develop them into therapeutics, diagnostics, or devices. These companies hope to mitigate the risk of

discovery and product development. "By selling services and tools, platform companies avoid the burdensome regulatory approval process and can reach profitability faster than fully integrated companies. Some platform companies are able to boost profitability by negotiating royalties on therapeutics or devices developed by others who use their tools or services"[73]. Two positive examples would be Alnylam and Epigenomcs, two examples that were not successful after a couple of years were MWG Biotech and Genescan.
The pitfall of such a business development approach would be to become a commodity company after a while and due to low entrance hurdles the competition is everywhere. In other words this approach would again require innovation and research to differentiate from the "me toos", which in turn would compromise this kind of business model.

Mixed Corporate Models:

There is no single most effective route for sustainability, profitability and growth, and therefore also mixed models exist "where companies do both outsourcing and integrating[73]". "Mixed-model companies run two businesses at once"[73]. Morphosys, a platform company founded in 1991 for example, uses such a mixed model. It started with a sophisticated technology called HuCal to select specific antibodies out of a library containing millions of antibody variants. These selected antibodies were sold or out-licensed to pharmaceutical companies. In 2008 the company entered in clinical trials with a proprietary therapeutic antibody and the program is currently being tested in a phase 1b/2a trial.

## COMPANION DIAGNOSTICS

Approvals for potential blockbuster drugs are becoming rare these days and the patent protection periods of many "billon sellers" will end in this decade. Pharmaceutical companies are trying to find new routes for a return of their long-lasting R&D investments. It seems that personalized medicine, molecular targeted therapies and companion diagnostics could be such routes.
One of the first examples of a molecular targeted therapy was the drug Iressa from Astra Zeneca that was initially approved for non-small-cell lung cancer (NSCLC) in the US. In contrast, an EU pending approval was withdrawn when a confirmatory Phase 3 study showed no survival benefit with Iressa compared with placebo. A closer analysis of the data revealed however, that some patients responded exceptionally well to the drug and, "furthermore, that these patients had activating mutations in the epidermal growth factor receptor (eGFR), providing a predictive biomarker of efficacy for the product"[76].
The Business development of Astra Zeneca formed a partnership with DxS (now Qiagen) to provide a companion diagnostic for use with Iressa and the drug is now approved also

in the EU for a defined type of NSCLC showing these mutations in the eGFR. Other examples of target therapies comprise GeneXpert RUO for BCR-ABL from Cepheid, the HercepTest for HER-2 from Dako, or TheraScreen for KRAS from TrimGen.

The area is anticipated to grow. GlobalData estimated the companion diagnostics market to be worth $790 Million in 2011 and to grow at a CAGR of some 20% during until 2018[77].

As shown with Iressa, the development of a companion diagnostic in late clinical development can bear some risks. Astra Zeneca's was fortunate as the company's approach was not taken proactively but rather driven by opportunity to make the best out of facts and situation. For a Biotech company, a co-development would appear to be the preferred approach and

> "the progression of a predictive biomarker to a companion diagnostic should follow the same development timeline as the drug it is to be used in combination with". Co-development will limit the impact that the lengthy companion diagnostic test validation process may have on the launch date [of the therapy] (….) and ensure that the two can be launched simultaneously. In addition, fewer patients will need to be enrolled on late-stage trials making drug development more economical by reducing costs and duration. In addition, clinicians would be able to select the same patients immediately once the drug is approved."[76]

The shift in the oncology market challenged regulators to draft new guidelines for the development of companion diagnostic tests. In 2011 the FDA had issued a "Draft Guidance for Industry and Food and Drug Administration Staff - In Vitro Companion Diagnostic Devices"[78]. In this paper the agency states that it may not approve "a novel therapeutic product or new therapeutic product indication for use with an IVD companion diagnostic device if the IVD companion diagnostic device is not approved or cleared for that indication."[79] However, "in cases where the therapy is intended to treat a serious or life-threatening disease or condition for which there is no available or satisfactory treatment and when the potential benefits outweigh the risks of not having a cleared or approved companion diagnostic, the therapy could be approved first while the companion diagnostic may be approved or cleared later through the appropriate device submission process."[80]

The EMA has released a reflection paper[81] in 2011 on use of "genomic markers" in the development and testing of human medicines for public consultation. The paper also addresses aspects of companion diagnostics shortly.

## BIOMARKER STRATEGY

Case setting – Storyline:

*Fleximab believes that the treatment of MRD will not only be adopted widely in Europe, but also with a lag phase in the US, as compelling long term outcomes data will become available. Thus – despite the FDA opinion (see above) - efforts will be taken to establish MRD testing in the US through an external entity with the expectation that both an Investigational Device Exemption (IDE) and Premarket Approval (PMA) will be needed. Such a companion diagnostic could be applied globally when available.*
*One of the strategic imperatives in FlexiMab's business development would be to expand into high medical need segments of other hematological diseases such as Non-Hodgkin lymphoma (NHL) with a focus on diffuse large B cell lymphoma (DLBCL). This patient population is approximately 2-3 times larger than that of ALL.*
*It would be tempting to speculate that molecular stratification of patients in this indication could be aligned with a TwinBite7 treatment to achieve better response rates in patient sub-populations. In addition such a "theragnostic" approach would be helpful to generate hypothesis and stratify patients in some way.*

## EARLY ACCESS TO DRUGS - NAMED PATIENTS & COMPASSIONATE USE

Case Setting – Storyline:

*Having addressed the prerequisites and options for expedited approval pathways (compare e.g.* Table 10*, p60) Hal wants to discuss whether a Named Patient Use (Compassionate Use) would support the value story or could even create financial return pre launch. Due to the success of study FlexiP2 that was made public at ASCO and ASH with subsequent press releases, the company had received requests for treatment options from three European investigators. In all cases the patients would not fulfill the inclusion criteria for ongoing studies. Hal suggested that - if at all - Named Patient treatment should be done only at sites having reasonable experience with both disease and drug. Germany had enrolled most of the patients and key opinion leaders in ALL were early adaptors participating as investigators in the first clinical trials with FlexiMab. Hal and the team were well aware that decisions on a case-by-case basis might put all people involved at FlexiMab in an ethical dilemma.*
Compassionate or Named Patient Use have many facets that may jeopardize or support the value proposition of a company with products still under evaluation in clinical trials. It

may also be used to generate early revenues but could become a cash burden also. Therefore, it is a Business development responsibility to support the executive management in that decision making process.

Compassionate Use is generally understood as the provision of unauthorized drugs with assumed benefit to patients having a "chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who can not be treated satisfactorily by an authorised medicinal product".[36]

The basic theme is that the lack of treatment alternatives and a poor prognosis justify accepting a higher degree of risk that might otherwise be intolerable.[82] Compassionate Use[ix] provides expanded access to products still under investigation, but its only objective is to help the patient and not to investigate a scientific hypothesis.

The legal basis for Named Patient schemes in the EU is Article 5(1) of Directive 2001/83/EC providing sponsors with an exemption to the general requirement for a marketing authorization. According to that article, a member state

> "*may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health care professional and for use by his individual patients on his direct personal responsibility."*

The interpretation of Article 5 remained a national responsibility for many years. Since regulation (EC) 726/2004, as part of the new EU medicines legislation came into force in 2005, some member states have introduced a possibility to authorize Compassionate Use programs for groups (or "cohorts") of patients in line with article 83 of the regulation. Interpreting these two legislations in the strict sense means that "using an unauthorised medicinal product for Compassionate Use on a Named Patient basis (Article 5 of Directive 2001/83/EC) does not fall under the scope of Article 83 [(EC) 726/2004][83]" as this Article refers to groups of patients only.

Still the legislation is not harmonized. In Germany, Compassionate Use was introduced into the legislation with the 14th amendment of the German Medicines Act (AMG) and modified by the amendment of the act in 2009. While other countries had their national ways to implement the law, this was only recently implemented in Germany by the 2010 "Ordinance on Medicinal Products for Compassionate Use – AMHV", which regulates the details of article 83.

It is an interesting notion in this patchwork of legal distinctions that in some countries a temporary license is granted and not an exception to the general obligation for a MA. This in turn may allow the manufacturer to charge for the cost of the drug to the patient, the hospital or the regional/national health service. This could be indeed the case in Italy

[ix] Compassionate use in the scope of Reg. EC 726/2004 is often called also (sometimes falsely attributed) as "named patient", "nominative prescription", "temporary use licence", "humanitarian use", "ATU", "special Need", "Uso Compasivo".

(legislation 648) and France (ATU)[x].

Case Setting – Storyline:

*Hal summarized the input from Business Development, Regulatory, Medical, and Legal teams:*
*A Compassionate Use program needs to be conducted free of charge in Germany and would require administrative efforts (e.g. reporting to the EMA, treatment protocols, insurances). However, besides the fact that such programs could be a means of building relationships to future customers and to bridge the time gap between filing and approval it would provide no added value. Rather the risk would be imminent that this option in a "real world setting" - i.e. outside of clinical trials might be dangerous (e.g. inexperienced physicians, inappropriate handling of serious AEs such as CNS events).*
*In Germany the legal basis for a Named Patient Use would be Article 5 of Directive 2001/83 EC in conjunction with section 34 of the German Criminal Code that "anybody who takes an action in an extra-legal emergency to help somebody does not act unlawful".*
*In order to differentiate between Compassionate Use and Named Patient Use the team consulted a Flowchart published by the PEI[84].*
*As Article 83 in Regulation EC 726/2004 refers to "groups of patients" the question must be answered how such a group is constituted. The EMA Compassionate Use guideline provides an answer: "`Group of patients´ can be interpreted as any set (i.e. more than one) of individual patients that would benefit from a treatment for a specific condition".*
*Given all these uncertainties and ambiguities Hal and his teams rejected the option of an early access to TwinBite7 based on Compassionate Use programs or Named Patient Use for the time being.*

## **CASE STUDY DECISION ANALYSIS** (MONTE CARLO SIMULATION)

Effective documentation ensures overview and clarity in development projects and is a contributing factor in achieving the development goals.
"If it is not documented, it is not implemented" - this well-known statement of inspectors and auditors is an axiom. A process that may exist in reality is inexistent in this view if not described in writing.
Documentation promotes information security, confirms prior art ensuring the traceability of development steps and it may even avert greater damage to the company: In the ´90s of the last century, Genentec sued Boehringer Mannheim for litigation of a basic

x Renato Dellamano, NME (http://www.m2econ.com), Pricing & Reimbursement consultant, personal communication.

patent related to the tissue plasminogen activator, tPA, a potential blockbuster drug. By retrieving the respective date for the invention from the files of the laboratory books, Boehringer could indeed prove to have prior art (only a few days) for the invention. Subsequently, the case was closed.[xi]

Planning an eDMS & eCTD Project:

The current process for regulatory submissions includes the compilation of numerous drug development and submission relevant documents. These documents reside in various parts of the organization and are not always readily accessible for review and re-use. If a company does not have harmonized standards or requirements across projects and products for document authoring, retention, and retrieval, it is difficult for authors/contributors to manage information in a consistent, efficient manner. This is especially true for regulatory submission documents. The need to provide these documents in an eCTD format is strongly recommended in the US[85] and binding in the EU[86]. Although an eDMS is not mandatory for a submission, the impact of not initiating this project could result in delays and might bear the risk of regulatory non-compliance producing submissions. In addition, not to implement such a project may impose an increased and continued burden on the company, as product dossiers would have to be compiled manually. This translates into decreased staff efficiencies, as manual processes are not scalable. The risk to the company will increase over time due to a boost of documents to be filed for submission.

Case Setting – Storyline:

*Monte Carlo Simulation for eDMS/eCTD Project:*

*From his Big Pharma background Hal knows about the importance of documentation - and during his last assignment in a larger enterprise the technology was ready for both an electronic document management system (eDMS) and an electronic Common Technical Document (eCTD).*

*The implementation of both systems was a painful process, but backed from executive management and at the end most people were happy with the tools.*

*Hal asked both Core Teams, RA and QA for a situation appraisal related to Filing Readiness of TwinBite7 and it was obvious that the company has not yet arrived in the digital word of documentation:*

[xi] G. Schumacher, Boehringer Mannheim/Roche, personal communication

| ***Threads and Opportunities*** | ***Separate concerns*** | ***Seriousness*** |
|---|---|---|
| *Documentation not ready for filing* | *eCTD not ready, an eDMS is not in place, the computer systems are not validated* | *Serious as EMA, will not accept paper versions, FDA strongly re-commends eCTD; Pot. buyers /partners prefer eDMS; Preapproval inspections will regard that deficiency as critical* |
| ***Urgency*** | ***Growth*** | ***Locate action steps*** |
| *Although regulatory filing is some years away eDMS is time demanding; Even a hosted solution would also need significant preparation of core documents* | *Problem will increase as documentation increases in later stages of development* | *All departments, RA takes eCTD lead, QA takes eDMS lead* |

*Hal decided to ramp up an eDMS/eCTD project. He took the opportunity to inform all employees about the new endeavor and stressed the importance for the regulatory filing efforts. In his memo he introduced an eDMS/eCTD working team chaired by a RA and a QA project manager and being constituted of members from all line functions.*

*The eDMS/eCTD working team held a kick off meeting and agreed to the following steps:*

*a) Approve High Level User Requirements Specification eDMS /eCTD*
*b) Setup of a list of criteria for eDMS/eCTD vendor selection*
*c) Market analysis: Get first price estimate from vendors, Complete eDMS/eCTD vendor selection: decision for 1 vendor*
*d) Hold presentation to management board*
*e) Contract negotiation and fine tuning of terms*
*f) Purchase eDMS + related services*
*g) Implement and validate eDMS and eSubmission document management*
*h) Plan and start implemention of migration of legacy eSubmission documents*
*i) Define eCTD standards and processes, Roll-out eCTD authoring templates*
*j) Train users*
*k) Explore expansion eDMS to other business areas / processes*
*l) Complete migration of legacy eSubmission documents*

*Hal identified six steps that bear risks in terms of time delays. These are market analysis, contract negotiation, implementation and validation of software, legacy document migration, user training, and complete legacy migration.*

*He asked Business Development and Finance to run a Monte Carlo simulation based on these steps and additional issues that would help to estimate both time and cost associated with this new (sub-)project(s).*

*Associated with each step is a Most Likely, Best Case, and Worst Case scenario in terms of number of weeks required to complete the stage. In addition, the teams have also identified seven different events, along with the probability of their occurrence, that could delay the project: Customization (75% chance), employee sickness / vacation (75% chance), employee change (5% chance), complications with validation (10% chance), equipment failure 5% chance), adding new user requirements (75% chance) and the possibility of legal issues (5% chance). All seven potential delays are also associated with*

*the three scenarios (Likely, Best, Worst Case). The model output*[xii] *is presented on p61 in* Figure 6 Monte Carlo Analysis of eDMS/eCTD Project*. Based on 1.000 runs per uncertain variable the model suggests adding 22 additional weeks and some US$66.000 on top and a >97% probability to finish the project within a total of 18 months.*

## CASE STUDY DECISION ANALYSIS (NEW INDICATION)

Case Setting- Storyline:

*Based on the promising data in the first Phase 2 trial in ALL with TwinBite7, the company could recently close a series E financing of some €50 Million.*
*Hal, knowing how drug development might fail wants to advance the FlexiMab technology to solid tumors in order to fuel the development pipeline as quickly as possible.*
*He passes the task over to the project manager of TwinBite9, and his request is rather demanding:*
*"I think the grace period for this company is over. Our investors get impatient – they want a return – the earlier the better. We know that we need a compelling pipeline to increase the company value. For this I want a solid tumor indication in development. We need to make up our mind what indication we are aiming at. I need some good news for the public too. Check where we stand and how we could advance TwinBite9 most rapidly in a solid tumor indication. I have allocated a budget of €1.5 Million for finalization of preclinical and Phase 1 studies. You have 4 weeks for this. Take the resources you need. You have my full support."*

*The PM is inviting the Core Team to a kickoff meeting, objective:*

> *"Advancing in solid tumor indications - fuel FlexiMab's pipeline - what do we have, what do we need.*

*The situation appraisal* revealed the following[xiii]:

| ***Threads and Opportunities*** | ***Separate concerns*** | ***Seriousness*** |
|---|---|---|
| *No Plan/ lacking criteria of how to proceed with platform development* | *The approach of developing new indications is not systematic* | *Serious, only filled pipeline contributes to company value, Only if advanced clinical candidate in place a failure with lead medicinal product could bolster the company* |
| ***Urgency*** | ***Growth*** | ***Locate action steps*** |
| *all development steps require significant amount of time, especially clinical dev* | *Any delay will increase the time and development gap to lead medicinal product* | *Core Team 1 (solid tumors)* |

[xii] Monte Carlo simulation was calculated with RiskSolver Pro (a fully functional free trial evaluation software) based on a model of "Software Development Cost"; http://www.solver.com/
[xiii] All tools and decision analysis steps were taken and modified from Joop & Wilkens course script, Master Course 11, 2009, Module xii.

*The necessary first step in the Decision Analysis is to clarify the purpose of the decision. The Core Team agreed to the following decision statement:*

*"Identify therapeutic indication(s) with optimal fit to TwinBite9".*

*The project manager provides the CEO's message to the team and describes the further steps of the decision analysis asking them to come back with a list of criteria to proceed with a decision analysis for the next meeting.*

*Step 2 and Step 3: Development criteria and Categorization of the decision criteria in „Must" and „Wants" – criteria.*

*The team comes back with the following – still unsorted - list of criteria:*

*Clinical rational: Expression level of EPCAM on tumor cells higher than on normal tissue*
*Existing clinical correlates to EPCAM: At least two studies showing positive outcome*
*Phase 1 as early as possible in not more than one year from now*
*Budget must not exceed €1.5Mil till end of Phase 1 and total budget must not exceed 50Mil*
*Existing clinical correlates to EPCAM: more than two studies showing positive outcome*
*…….*

*A MUST criterion is mandatory for the project. MUSTs are either fulfilled or not. If not this would be a no go decision for the project. In contrast the WANT criteria are not that digital and need to be classified.*

*The result of the categorization of the decision criteria is shown below:*

| | ***Development criteria*** | ***Must/ Want*** |
|---|---|---|
| | *Clinical rational: Expression of EPCAM in tumors higher than on normal tissue* | *MUST* |
| | *Existing clinical correlates to EPCAM: At least 2 trial showing positive outcome* | *MUST* |
| | *Phase 1 in not more than one year from now* | *MUST* |
| | *Budget must not exceed €1.5Mil till end of Phase 1* | *MUST* |
| | *Epidemiology: High incidence of disease* | *WANT* |
| | *Low competition* | *WANT* |
| | *High Pricing* | *WANT* |
| | *Ideal combination: no overlap toxicity and different MoA on tumor cells* | *WANT* |
| | *Animal model for indication in place* | *WANT* |
| | *Low development costs* | *WANT* |
| | *Low development time* | *WANT* |
| | *Interest of potential partner already exists* | *WANT* |
| | *High medical need (addressed by competitors but remains unsatisfactory)* | *WANT* |
| | *Potential use as first line therapy* | *WANT* |
| | *Surrogate parameters available* | *WANT* |
| | *Easy definable endpoint* | *WANT* |

*Step 4: Assign Weights to the „Wants" – criteria*

*Furthermore, the MUST criteria should be converted into WANTs in order to assign them with a weight. Thus, the converted MUSTs in our case should read:*

| ***Must Development criteria*** | ***MUST into WANTS*** |
|---|---|
| *Clinical rational: Expression level of EPCAM on tumor cells as high as possible* | *WANT* |
| *Existing clinical correlates to EPCAM: >2 studies showing positive outcome* | *WANT* |
| *Phase 1 as early as possible* | *WANT* |
| *Cost as low as possible till end of Phase 1* | *WANT* |

*The project manager asks the team to weight the criteria on a scale from 1-10. To avoid any bias resulting from "group dynamics" the team should assess each criterion and weigh it against the next in the list. Doing this with a list of 14 criteria would result in 91 decisions. The analysis and results are shown in* Figure 7 Decision Preference Matrix *on page 62.*

*Step 5: List Alternatives*

*The project manager asks the team to prepare alternatives in terms of indications which will be assessed against all objectives for the upcoming meeting and asks them to come back without any papers. The team provides the following suggestions:*
*"Colorectal-, Ovarian-, and Pancreatic Cancer".*

*Step 6: Check of all known alternatives against the „Must" – criteria and „Wants" – criteria.*

*In this step the team is asked to evaluate the WANTS criteria in the decision analysis. Clearly they are not of equal importance. To keep things simple they were classified on a 1 - 10 scale (or with only 3 alternatives the best choice could be evaluated with a 3 and the others measured against the "best choice" with 2 and 1 for example). Each of these classifications is multiplied with the result of weighting from the list of criteria shown in from* Figure 7*. As such, all alternatives may be compared against each other.*

*First, the alternatives are screened out that fail to meet the minimum requirements (i.e. MUSTs). Colorectal CA is too expensive and seems to take longer than the other alternatives for preclinical evaluation and Phase 1 studies.*
*Now the team analyzes which of the (remaining) alternatives satisfies the WANT objectives best. The results are presented in* Figure 8*, p63.*
*Pancreas and Ovarian are the best choices and Hal requests a risk analysis regarding the two indications.*

*Step 7 Risks/adverse consequences*

*In this step the adverse consequences have to be assessed. The team reflects on the risks with the two alternatives. They think of all issues that could go wrong and how likely it is. They also reflected on the seriousness by asking if it happens, how serious it will be.*
*They decided to classify these issues according to probability (P) and seriousness (S). The Probability and the Seriousness should be classified in high (H=3), medium (M=2) and low (L=1) scales. They discussed the alternatives and put the results down in* Table 12*, p64.*
*As both indications are potentially orphan, the overall risk scoring does not differ very much. There are some differences, however. The prevalence (and incidence) for Pancreatic Cancer is even lower than for Ovarian CA. The collective median survival time of all patients is only 4-6 months for Pancreatic CA. Thus, it might be easier to define overall survival as the primary endpoint. The probability of survival or cure in ovarian CA is much higher.*
*On the other hand, assessing the clinicaltrials.gov database suggests that there are more than 800 clinical studies conducted for Pancreatic CA worldwide.*
*This could either mean that there is much competition someday, or that Pancreatic CA is an unmet medical need which today is incurable.*
*The team spent thoughts on measures how these risks can be minimized and the results are presented in* Table 13 Risk Analysis of Alternatives*, p65.*

*Step 8 Decision/ Best balanced choice*

*From the above assessment, the team decides to start the further development with Pancreatic Cancer as an indication.*
*In Pancreatic Cancer there are only 3 approved drugs on the market. A combination partner should be envisioned having a different MoA and an overlapping toxicity profile to increase efficacy and lower the number of additional adverse effects.*
*In oncology, overall survival (Gold standard), progression-free survival, time to treatment failure, time to progression are primary endpoints. In pancreas CA the median time of survival is only four months.*
*Thus, a hard clinical endpoint is addressable also in a small study population and prolonging the survival by several weeks would prove a statistically significant outcome - even with a limited number of patients.*

# DISCUSSION & OUTLOOK

In daily life risks are perceived as uncertain events having a negative impact. It is often ignored that this uncertainty involves also a positive component, as there is always a chance that things turn out better than anticipated.

Donald Rumsfeld – in a different context - described uncertainty perfectly:

> „[T]here are known knowns; there are things we know we know. We also know there are known unknowns; that is to say we know there are some things we do not know. But there are also unknown unknowns – there are things we do not know we don't know" [87] (February 12, 2002).

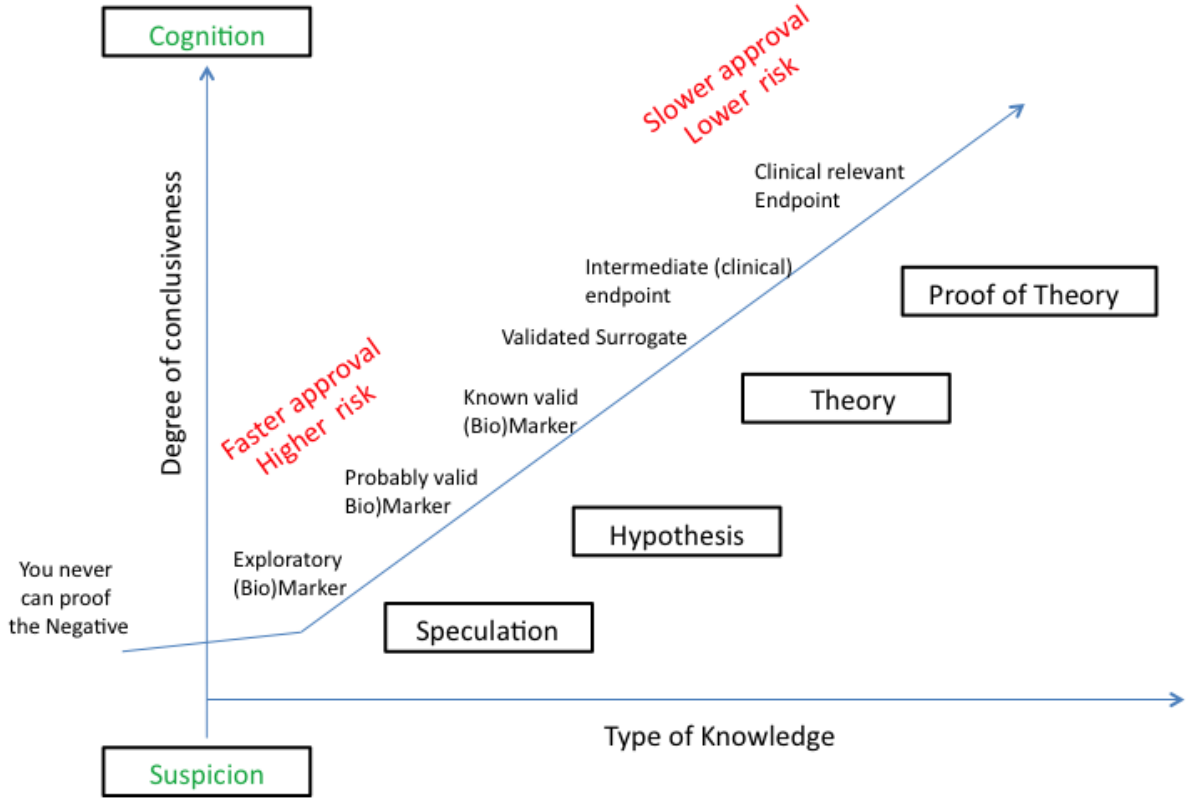
"Knowns are things that are certain, such as death. Known-unknowns are uncertainties that can be identified but their effects are not known. Last, unknown-unknown is something that cannot be imagined, such as AIDS before the first case was reported"[6].

In drug development there are several main avenues of uncertainties and risks.
One is related to the uncertainty whether the anticipated business case of the drug ever becomes a reality. This is a systemic risk that cannot be influenced and this is the reason why NPV calculations consider a discount rate well above 15% to compensate for this uncertainty.
A second avenue is related to risks of the drug itself and its Mode of Action, which are commonly addressed as drug safety risks. These are risks that are also inherent but they can be mitigated - e.g. in a cancer therapy the risk of treatment discontinuation is moderated by antiemetics or the CNS events related to the therapy of TwinBite7 may be addressed by prophylactic treatment with PPS or dexamethasone.
Another avenue of risk, which is not intrinsic to the drug however, is given by the way we deal with knowledge and the expectations (or hopes) we associate with a therapy.
Whether a drug will do harm or whether it will show a positive risk-benefit can only be stated with virtual certainty ex post using the methodology of evidence based medicine.
To shorten this lengthy process of cognition, clinical science (and society) have invented the concept of surrogate endpoints.
The advantage of surrogate endpoints is quite obvious: They save time and money and allow for rapid decision making[88] as they can be assessed after a relatively short period of time and measured easily with high precision.
Support or rejection of surrogates impose an ethical dilemma as one the one hand patients could experience serious side effects without an anticipated benefit, but on the other hand would be withheld from a potentially beneficial therapy.

Stefan Lange, IQWiG's Deputy Director states: "Consequently, conclusions on the benefit and harm of new drugs will be characterized by some degree of uncertainty".[89]

This degree of uncertainty, using different biomarkers as endpoints, is shown below as a function of type of knowledge and corresponding degree of conclusiveness[xiv].

The clinical science is advancing rapidly and targeted therapies, surrogate endpoints, companion diagnostics, and biomarkers offer new ways for pharmaceutical companies to develop "The right drugs for the right patients". That these benefit from the therapy and risks are assessed and balanced by regulators, health assessment agencies and payers lies in the legitimate expectation of the informed individual this industry is all about – the patient.




[xiv] modified for this purpose from Straeter, DGRA Master Course 11, 2009, Module II, slide 83 (m02-staeter1-pdf).

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[7] Hal is pretty much an "Analytic" and can be very convincing. In fact some (former) employees say "Hal" would stand for "Heuristic Algorithmic". This is because the CEO wants to be involved in details and requests decisions based on ratio and facts similar to famous computer HAL-9000 in "2001: A Space Odyssey".

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# APPENDIX 1 FIGURES AND TABLES

Figure 1 Fleximab's Lines of Responsibility & Decision Makers

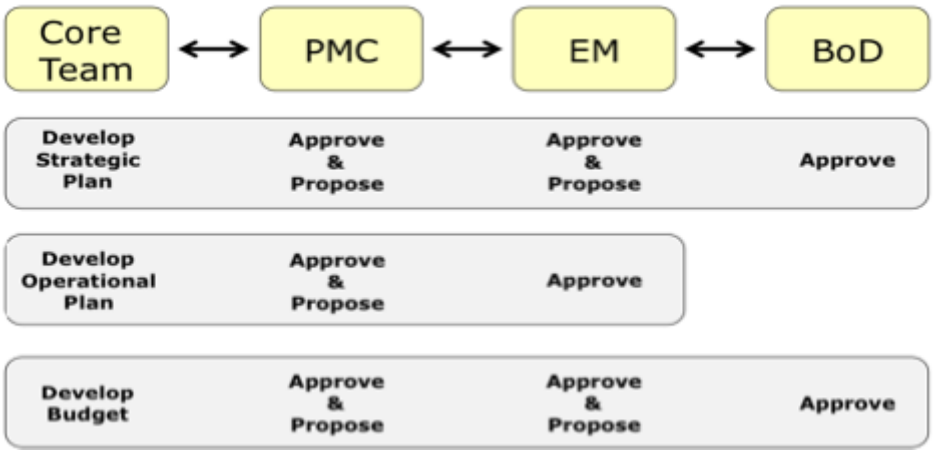
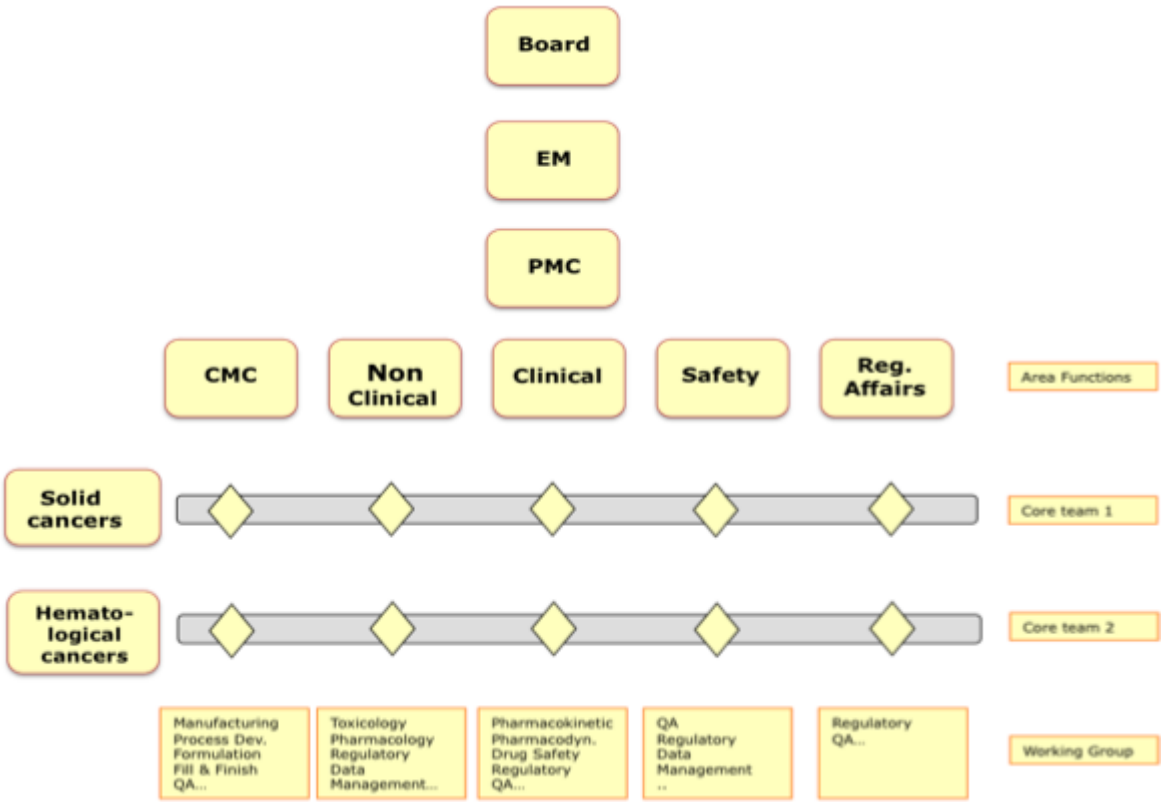



Figure 2 FlexiMab's Organization & Matrix Structure




(EM: Executive Management)

Figure 3 FlexiMab's Process of Drug Development and Gate Controlled Decisions

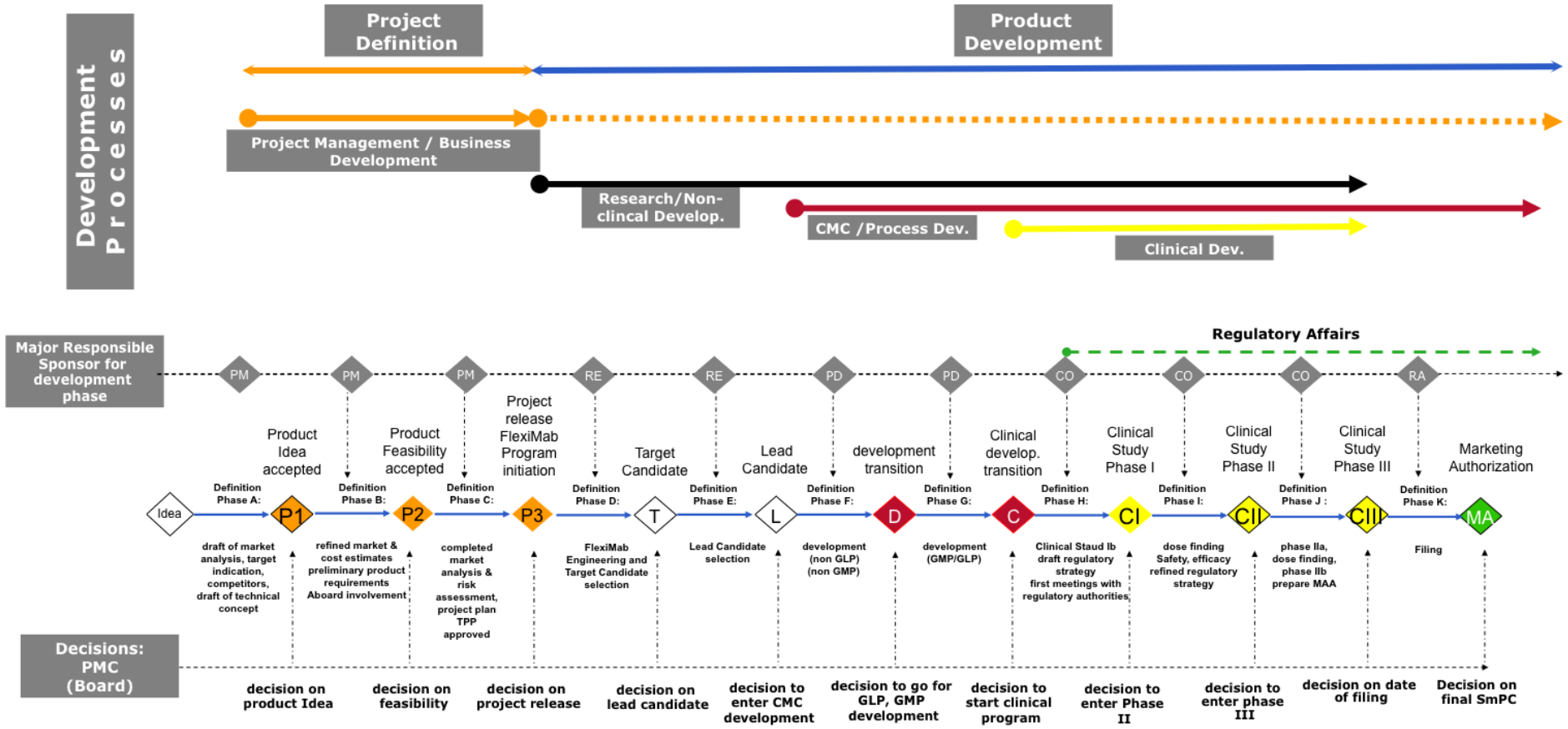


Figure 4: Impact - Probability Matrix

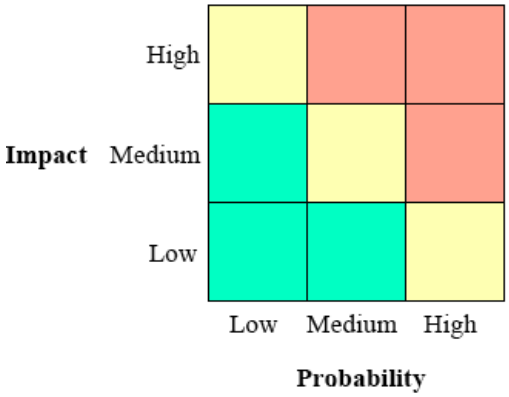



Figure 5: Risk isobar presents the acceptable level of risk cited in[6]

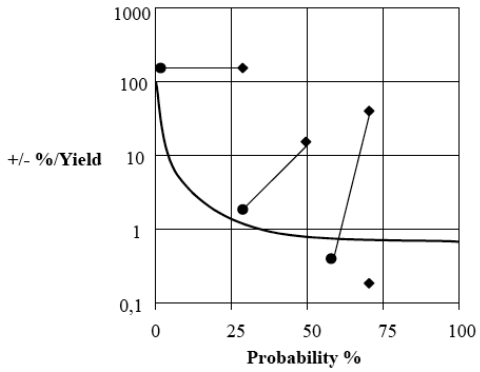



Table 1: Risks in Drug Development

(Modified according to[6,27])

| **Project management** | **Discovery** | **Regulatoy** |
|---|---|---|
| Schedule Cost<br>Scope<br>Design errors | Platform technology<br>Mechanism of action<br>Durability of concept<br>Predictability of targets and models | Regulatory changes<br>Product compliance<br>Risk/benefit ratio<br>Product compliance<br>Future changes in regulatory regime |
| **Commercial** | **Project operations (Preclinical/ Clinical)** | **Business environment** |
| Product value<br>Competitive advantage<br>Peak sales<br>Interest rates<br>Currency<br>Cash flow credit<br>Financial markets<br>Contractual<br>Litigation<br>Cost of goods<br>Launch risks | Patient population<br>Clinical end points<br>Safety / Efficacy<br>Comparators<br>Predictability of trials<br>Pharmacokinetics<br>Formulation and scale-up<br>Pharmacology<br>Analytics<br>Process development | Competitors<br>Customers<br>Partners<br>Technology change<br>Political change<br>Legal change<br>Markets restructuring<br>Availability Knowledge<br>Intellectual property challenge |

Table 2 Differences of Biotechs and SMEs in the conduct of projects

(own research)

| **Drivers - Processes - Mindset** | **SME** | **Big Pharma** |
|---|---|---|
| Drug development | Manage one (a few) drug candidate(s) | Manage a portfolio of drugs |
| Keep development time to a minimum | Pivotal phase 2, conditional /accelerated approval | Comparative Phase 3 (high disease prevalence) |
| Be early on the market with a first-in-class product | Put long term strategic plan behind attractive exit scenario (trade sale, share deal) | Greater sustainability. Long term efforts to develop and launch a drug |
| Reduce development times and development costs | Limits itself to what is necessary, tries to succeed with one shot, stick to minimal requirements (pivotal Phase 2, accelerated approval) | More relaxed as far as costs are concerned |
| Find partners, liaise | Find partners to fund projects, Sales & Marketing | Find partners for research and early development |
| Clinical program | Rarely more than a few Phase 2 studies and hardly Phase 3 | Support of comparative Phase 3 trials |
| Keep development changes within cost and time limits | Hardly any backups, no redundancy, no plan B, no second source | Probably more backups (e.g. R&D and manufacturing in more than one country) |
| Risk management | Due to limited resources spent more time proactively | More relaxed as far as risks are concerned |
| SmPC, TPP | Narrow or orphan indication, niche products | Have a broad range of claims within the TPP and ultimately in the MA |
| Sense of urgency (sense of survival) | Leads to extremely diligent R&D and or to bet everything on one card (e.g. 1 dose finding study with 2 doses) | More luxury situation; e.g. dose escalation more refined) |
| Communication | Directly over hierarchy levels | Munch slower and more challenging; needs to be organized |
| Mindset /Attitude | "Whatever it takes" | More "relaxed" failures will not generally jeopardize enterprise |
| Driven by opportunity | Strategic decisions are often changed due to inside or outside events | Pursue the route already embarked |
| Executive Management awareness | On the project level | On a "higher" i.e. portfolio level |
| Budget | Overruns can be more destructive to small companies | Have enough resources to cover overruns |
| Time to market launch | Probable less experience in late stage clinical trials, filing (CTD) and launch preparation | More efficient in late stage clinical trials and product launch |

Table 3: Tasks of the Project Manager

- Leading Core Team
- Implement project strategy as defined by Executive Board
- Define and track project plan together with team
- Call for risk analysis
- Define resources and budget together with line management
- Monitor project progress and budget, anticipate potential problems or delays
- Coordination of activities
- Conflict management
- Coordinate establishment of regulatory and other project related documentation
- Check feasibility of project objective
- Prepare for start of project and hold kickoff meeting
- Discuss change process
- Support patent registration
- Define type, content and scope of project, development
- Generate project structure and coordinate with PMC as needed
- Organize and execute planned meetings and reviews, implement decisions and conditions
- Set appropriate priorities
- Generate schedules
- Generate manpower plan
- Generate resource plan
- Request and order application tools and resources
- Ensure adherence to specifications, regulations and guidelines
- Evaluate co-workers (CRO, contractors…)
- Provide respective change requests
- Immediately report situations that exceed the limits of the plan to PMC
- Call for risk analysis when unforeseen events pose a danger
- Check development results for adherence to the requirements
- Be prepared for meetings and reviews
- Verify the implementation of decisions and conditions resulting from meetings and reviews

Table 4: Tasks Project Management Committee

- Develop product strategy,
- Evaluate product ideas and decide on further actions,
- Review product feasibility results and decide on further activities,
- Review results of Project Planning phase and decide on further actions,
- Approve product development projects if necessary,
- Supervise product and project planning,
- Monitor milestones schedules, and development results in accordance with requirements (target specification, data sheet),
- Approve development changes (additional costs and delays) after specific approval,
- Request recalculation of Project Plan,
- Define objectives and priorities for project,
- Request risk evaluation,
- Check and share responsibility for project decisions,
- Delegate tasks and responsibility

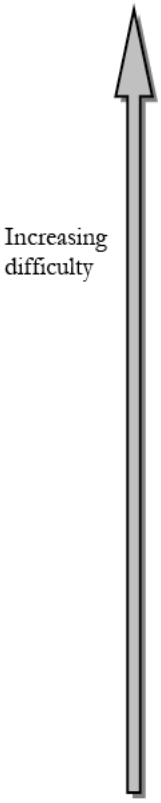
Table 5: Skills of a Project Manager

- Strong people skills,
- Development experience and understanding of the complexity of the development process,
- Common sense,
- Flexibility,
- Honesty, fairness and reliability,
- Ability to seek input from Core Team members and build consensus,
- Commitment to the project and objectivity at the same time,
- Leadership skills including respect for the contribution of others,
- Delegate tasks and responsibilities

Table 6 Surrogate Endpoints in Accelerated Approval

| Endpoint | Regulatory Evidence | Study Design | Advantages | Disadvantages |
|---|---|---|---|---|
| Overall Survival | Clinical benefit for regular approval | • Randomized studies essential<br>• Blinding not essential | • Universally accepted direct measure of benefit<br>• Easily measured<br>• Precisely measured | • May involve larger studies<br>• May be affected by crossover therapy and sequential therapy<br>• Includes noncancer deaths |
| Symptom Endpoints (patient-reported outcomes) | Clinical benefit for regular approval | • Randomized blinded studies | • Patient perspective of direct clinical benefit | • Blinding is often difficult<br>• Data are frequently missing or incomplete<br>• Clinical significance of small changes is unknown<br>• Multiple analyses<br>• Lack of validated instruments |
| Disease-Free Survival | Surrogate for accelerated approval or regular approval* | • Randomized studies essential<br>• Blinding preferred<br>• Blinded review recommended | • Smaller sample size and shorter follow-up necessary compared with survival studies | • Not statistically validated as surrogate for survival in all settings<br>• Not precisely measured; subject to assessment bias, particularly in open-label studies<br>• Definitions vary among studies |
| Objective Response Rate | Surrogate for accelerated approval or regular approval* | • Single-arm or randomized studies can be used<br>• Blinding preferred in comparative studies<br>• Blinded review recommended | • Can be assessed in single-arm studies<br>• Assessed earlier and in smaller studies compared with survival studies<br>• Effect attributable to drug, not natural history | • Not a direct measure of benefit<br>• Not a comprehensive measure of drug activity<br>• Only a subset of patients who benefit |
| Complete Response | Surrogate for accelerated approval or regular approval* | • Single-arm or randomized studies can be used<br>• Blinding preferred in comparative studies<br>• Blinded review recommended | • Can be assessed in single-arm studies<br>• Durable complete responses can represent clinical benefit<br>• Assessed earlier and in smaller studies compared with survival studies | • Not a direct measure of benefit in all cases<br>• Not a comprehensive measure of drug activity<br>• Small subset of patients with benefit |
| Progression-Free Survival (includes all deaths)<br>or<br>Time to Progression (deaths before progression censored) | Surrogate for accelerated approval or regular approval* | • Randomized studies essential<br>• Blinding preferred<br>• Blinded review recommended | • Smaller sample size and shorter follow-up necessary compared with survival studies<br>• Measurement of stable disease included<br>• Not affected by crossover or subsequent therapies<br>• Generally based on objective and quantitative assessment | • Not statistically validated as surrogate for survival in all settings<br>• Not precisely measured; subject to assessment bias particularly in open-label studies<br>• Definitions vary among studies<br>• Frequent radiological or other assessments<br>• Involves balanced timing of assessments among treatment arms |

Table 7 generic response strategies [26]




| Type of Response | Method of Dealing with Uncertainty |
|---|---|
| Convert risk to opportunity | |
| Avoid | Plan to avoid specified sources of uncertainty. |
| Modify objectives | Reduce or raise performance targets, change trade-offs between multiple objectives. |
| Transfer | |
| Share | |
| Insurance | |
| Prevent | Change the probability of occurrence. |
| Mitigate | Modify the impact of a source of uncertainty. |
| Develop contingency plans | Set aside resources to provide a reactive ability to cope. |
| Keep options open | Delay choices and commitment, choose versatile options. |
| Monitor | Collect and update data about probabilities of occurrence, anticipated impacts, and additional risks. |
| Accept | Accept risk exposure, but do nothing about it. |
| Remain unaware | Ignore the possibility of risk exposure, take no action to identify or manage risk. |

Table 8: Important actions steps and their time lines in the Prelaunch phase (own research)

| **Event/processoral element to be assessed /determined** | **EVENT / TIMELINE IN MONTHS** | **ACTION** |
|---|---|---|
| PIP / Interactions with the PDCO<br>Prepare PIP application | After Phase 1 | RA |
| Regulatory-strategy meeting<br>(As of 12/12 not yet implemented by EMA) | -18/ -24 | PMC |
| Invented Name<br>Register Invented Name in all (EU) countries | - 18 | Legal, Board |
| Eligibility for CP<br>Fill out and send eligibility request electronically (also required for products falling under "mandatory" provision) >10 days prior to next CPMP meeting | -18<br>(not later than -7) | RA |
| Preparing a value dossier for Health technology assessment) HTA | -12-<br>launch | RA, (Marketing) |
| Ask for Scientific Advice if<br>Pharmacopoeia monographs and/or guidelines do not address the question, or do not provide sufficient guidance<br>Company wants to deviate from the guidance available with respect to the development plan<br>Company requests a "conditional" MA<br>Company requests MA under "exceptional circumstances"<br>Company requests „accelerated assessment" | Anytime | RA<br><br>Support from<br><br>"Functional Area Heads" |
| Accelerated assessment procedure<br>If the medicinal product is intended to meet a major public health issue, provide rational for an accelerated evaluation (5-10 pages) by highlighting the three criteria:<br>• Seriousness of the disease (e.g. heavy disabling or life-threatening diseases) to be treated<br>• Absence or insufficiency of an appropriate alternative therapeutic approach<br>• Anticipation of high therapeutic benefit | -4/-6<br>(Ideally with 1st SA) | "Functional Area Heads" |
| Orphan Drug Designations<br>Prepare and compile some preclinical and/or clinical data to support the rationale for orphan designation. Prepare justification that the criteria laid down in Article 3(1) of RL 2001/83 are met and a description of the stage of development (including the indications expected) | Anytime<br>(Ideally with 1st SA) | "Functional Area Heads" |
| Meeting with Rapporteur and Co-Rapporteur before Filing; Prepare for discussion of critical file issues which may simplify the assessment<br>Inform the EMA Project team Leader who will try to participate to such a meeting via teleconference. In any case, minutes of such meetings should be provided to the EMA Project team leader | Before day 0; after (Co-) Rapporteur/ nomination | RA and "Functional Area Heads" |

Table 9 Expedited Approval Comparison US and EU
(own research; sources FDA, EMA website)

| | US | EMA | EMA |
|---|---|---|---|
| | **Accelerated Approval** | **Conditional Approval** | **Exceptional Approval** |
| **Legal basis** | 21 CFR Part 314, Subpart H (for drugs)<br>21 CFR Part 601, Subpart E (for biologics) | Art 14(7) and Recital 33 of Regulation (EC) No 726/2004 (Regulation (EC) No 507/2006 draft CHMP Guideline EMEA/509951/2006 of 5 December 2006 | Art 14(8) of Regulation (EC) No 726/2004 Guideline : PROCEDURES FOR THE GRANTING OF A MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES |
| **Prerequisites** | FDA may grant approval based on a surrogate endpoint that is reasonably likely…to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity."<br>• Serious or life threatening diseases<br>• Provides a benefit over existing therapies<br>• Subject to the requirement to verify benefit | May be granted although comprehensive clinical data have not been provided (preliminary judgment)<br>• Benefit/Risk balance is positive and<br>• it is likely that comprehensive clinical data will be provided and<br>• Unmet medical needs will be fulfilled and<br>• Benefit to public health of immediate availability | Comprehensive data cannot be provided (because of specific circumstances: rarity, medical ethics, state of scientific knowledge) |
| **Scope** | Serious or life threatening diseases | • seriously debilitating<br>• diseases or life-threatening diseases;<br>• medicinal products to be used in emergency situations…(WHO)<br>• orphan medicinal products | No information |
| **Provision for Approval** | Subject to the requirement to verify benefit | Comprehensive clinical data will be provided | Information on the safe and effective use of the product and will normally not lead to the completion of a full dossier |

| | US | EMA | EMA |
|---|---|---|---|
| | **Accelerated Approval** | **Conditional Approval** | **Exceptional Approval** |
| **Post marketing requirements** | "Approval… subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit…" (PMR)<br>"…Postmarketing studies would usually be studies already underway."<br>"…such studies must also be adequate and well- controlled."<br>"…The applicant shall carry out any such studies with due diligence" | Specific Obligations (SPO) " to provide further data; complete ongoing studies, or to conduct new studies, with a view to confirming the risk-benefit balance is positive, for example:<br>Pharmacovigilance data, confirmation of final clinical outcome for surrogate endpoints, long-term effects,.." | focus on safety studies |
| **Endpoints** | May be based on surrogate endpoints; | Concept of surrogacy exists;<br>Results of single-arm trials are the most problematic to interpret ⇒ high risk of rejection<br>RCT after approval not feasible ⇒ risk of remaining conditional indefinitely | No information |
| **Focus on outcome / follow up** | Efficacy | Positive benefit risk | Safety |
| **Application** | Requested by the applicant | May be requested by the applicant or proposed by the CHMP | may be requested by the applicant |
| **Conversion to normal Approval** | Fulfill Post Marketing Requirements | Fulfill Specific Obligations | Exists as a "normal" approval |
| **Authorization timeline** | Ongoing; assessment is by judgment (i.e. if new data comes in); no fixed renewal date or assessment | Authorization valid for one year (renewable) | Reviewed annually to reassess the risk-benefit balance; valid for five years (to be renewed one time) |
| **Withdrawal or other action with regard to Approval** | A postmarketing clinical study fails to verify clinical benefit;<br>(2) The applicant fails to perform the required postmarketing study with due diligence;<br>(3) Use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the biological product;<br>(4) The applicant fails to adhere to the postmarketing restrictions agreed upon; | MA may not be renewed after first year<br><br>Suspend, revoke, withdraw or vary authorisation if a product is viewed as harmful or as lacking therapeutic efficacy | MA is may not be renewed after 5 years<br><br>Suspend, revoke, withdraw or vary authorisation if a product is viewed as harmful or as lacking therapeutic efficacy |

| | US | EMA | EMA |
|---|---|---|---|
| | **Accelerated Approval** | **Conditional Approval** | **Exceptional Approval** |
| | (5) The promotional materials are false or misleading; or<br>(6) Other evidence demonstrates that the biological product is not shown to be safe or effective under its conditions of use | | |
| **Regulatory enforcement** | Financial penalties up to 10 Mil. US$ if are not executed with due diligence | Financial penalties in case of infringement of the specific obligations | Financial penalties in case of infringement of the specific obligations |
| **Further specifics** | An indication approved under accelerated approval which has not yet verified clinical benefit with its post-marketing trials is NOT considered existing therapy. | A conditional marketing authorisation only applies to new marketing authorisation applications; does not apply to new indications submitted as part of a variation or extension procedure | |
| **Transparency** | ODAC open to the public | Scientific Advisory Group meetings are closed to the public – even for the sponsor | Scientific Advisory Group meetings are closed to the public – even for the sponsor |
| **Time to conversion to normal MA (oncology)** | ca 3,9 years to convert in average | Since 2006: 5 granted, one converted | |

Table 10 COMPARISON OF MECHANISMS TO HASTEN PRODUCT AVAILABILITY

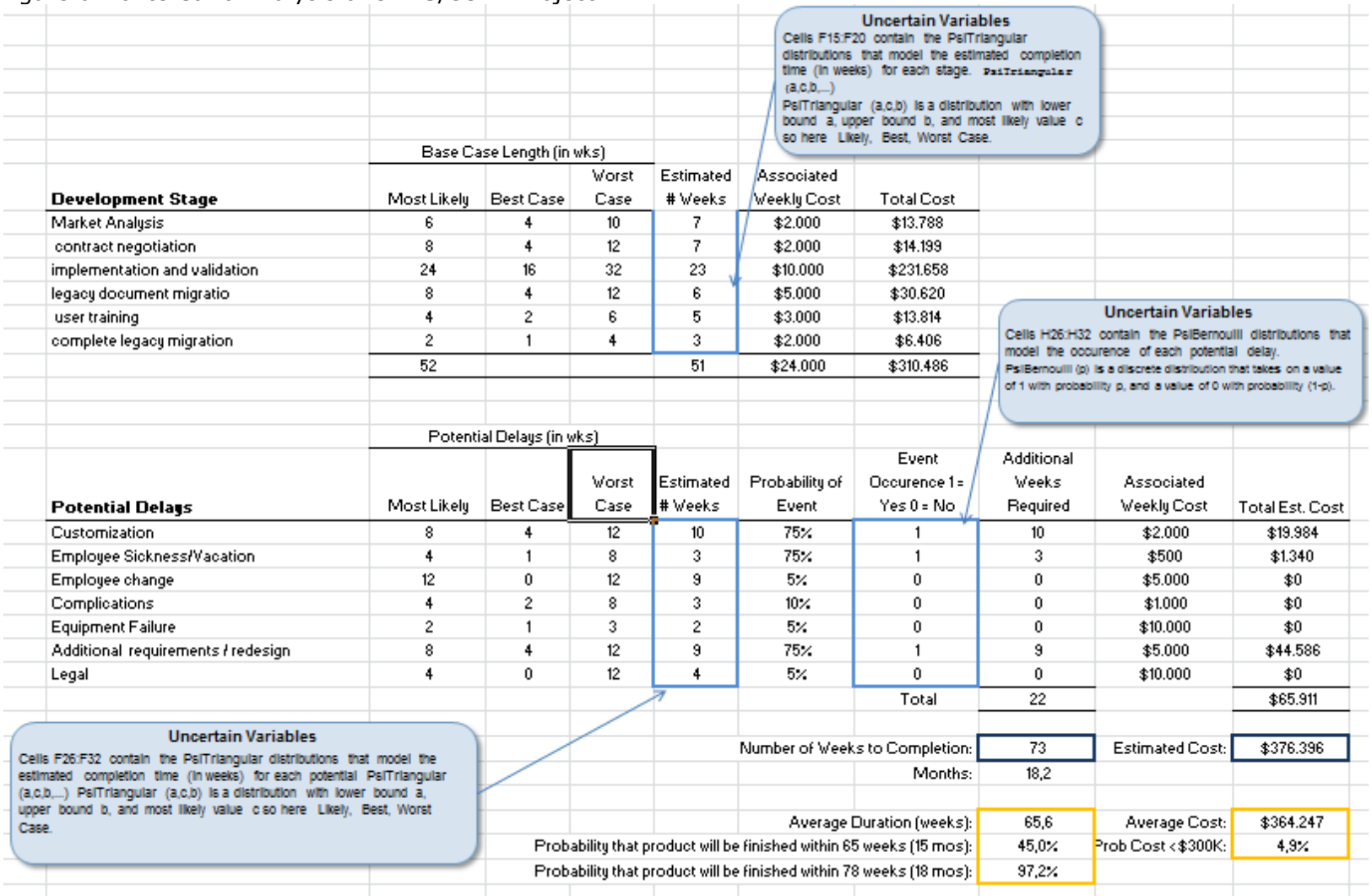
| | Accelerated review | Priority review | Fast track |
|---|---|---|---|
| Authority | 1992 *Rule*: 21 CFR 314 and 601 (In 1997, Federal Food, Drug, and Cosmetic Act (FFDCA) 506(b).) | 1996 *Agency Procedure*:<br>CDER Manual of Policies and Procedures<br>(MAPP) 6020.3; and<br>CBER Manual of Standard Operating Procedures and Policies (SOPP) 8405 | 1997 *Statute*:<br>FFDCA 506(a). |
| Procedure | [Not specified; presumably manufacturer would request and FDA would determine whether to grant.] | Clinical team leader of FDA review team, upon receipt of application, makes recommendation. | Any time before marketing approval, manufacturer requests designation; FDA grants if criteria are met. |
| Quality criteria | Serious or life-threatening illness | not applicable (n.a.) | Serious or life-threatening condition |
| | Potential to address unmet medical need | Major advance in treatment or treatment where no adequate therapy exists | Potential to address unmet medical need |
| | Adequate and well-controlled studies supporting use of surrogate outcome | n.a. | |
| Benefit during development | Adjusted trial outcome requirements | n.a. | Close communication with FDA |
| Benefit during review | n.a. | Additional attention; expedited review | Rolling review |
| Post approval requirements | Studies to extend results from surrogate to clinical outcome. | n.a. | |

Table 11 FDA Approaches to Expedited Drug Development

| | Accelerated Approval | Fast-track Designation | Priority Review | Breakthrough Designation |
|---|---|---|---|---|
| **Eligibility** | 1. Treat serious or life-threatening diseases<br>2. Provide meaningful therapeutic benefit over existing therapies<br>3. Surrogate endpoint reasonably likely to predict clinical benefit | 1. Intent to treat broad range of serious diseases<br>2. Potential to fill an unmet medical need | 1. Offer major advances in treatment over existing therapies | 1. Treat serious or life-threatening diseases<br>2. Early clinical evidence of substantial improvement over existing therapies |
| **Designation** | No formal process | Can be requested by sponsor at any time; FDA has 60 days to respond | Requested by sponsor at time of NDA/BLA submission; FDA has 45 days to respond | Can be requested by sponsor at any time after IND submission; FDA has 60 days to respond |
| **Clinical Development** | Conditional approval granted using surrogate endpoint from phase II trials or interim phase III data; controlled trials with hard clinical endpoints required to confirm clinical benefit | Earlier and more frequent communication | Not applicable | Abbreviated or condensed development; earlier and more frequent communication; delegation of senior reviewers and cross-disciplinary review team |
| **Review Process** | NDA/BLA data submitted in one package; standard 10 month review | Option for Rolling NDA/BLA submission. Official review clock begins when last module is submitted | NDA/BLA data submitted in one package; review time shortened to 6 months | NDA/BLA data submitted as they are accumulated; review time shortened |

## APPENDIX 2 DECISION ANALYSIS OUTPUT

Figure 6 Monte Carlo Analysis of eDMS/eCTD Project



**Uncertain Variables**
Cells F15:F20 contain the PsiTriangular distributions that model the estimated completion time (in weeks) for each stage. `PsiTriangular (a,c,b,...)`
PsiTriangular (a,c,b) is a distribution with lower bound a, upper bound b, and most likely value c so here Likely, Best, Worst Case.

| | Base Case Length (in wks) | | | | | |
|---|---|---|---|---|---|---|
| **Development Stage** | Most Likely | Best Case | Worst Case | Estimated # Weeks | Associated Weekly Cost | Total Cost |
| Market Analysis | 6 | 4 | 10 | 7 | $2.000 | $13.788 |
| contract negotiation | 8 | 4 | 12 | 7 | $2.000 | $14.199 |
| implementation and validation | 24 | 16 | 32 | 23 | $10.000 | $231.658 |
| legacy document migratio | 8 | 4 | 12 | 6 | $5.000 | $30.620 |
| user training | 4 | 2 | 6 | 5 | $3.000 | $13.814 |
| complete legacy migration | 2 | 1 | 4 | 3 | $2.000 | $6.406 |
| | 52 | | | 51 | $24.000 | $310.486 |

**Uncertain Variables**
Cells H26:H32 contain the PsiBernoulli distributions that model the occurence of each potential delay.
PsiBernoulli (p) is a discrete distribution that takes on a value of 1 with probability p, and a value of 0 with probability (1-p).

| | Potential Delays (in wks) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Potential Delays** | Most Likely | Best Case | Worst Case | Estimated # Weeks | Probability of Event | Event Occurence 1 = Yes 0 = No | Additional Weeks Required | Associated Weekly Cost | Total Est. Cost |
| Customization | 8 | 4 | 12 | 10 | 75% | 1 | 10 | $2.000 | $19.984 |
| Employee Sickness/Vacation | 4 | 1 | 8 | 3 | 75% | 1 | 3 | $500 | $1.340 |
| Employee change | 12 | 0 | 12 | 9 | 5% | 0 | 0 | $5.000 | $0 |
| Complications | 4 | 2 | 8 | 3 | 10% | 0 | 0 | $1.000 | $0 |
| Equipment Failure | 2 | 1 | 3 | 2 | 5% | 0 | 0 | $10.000 | $0 |
| Additional requirements / redesign | 8 | 4 | 12 | 9 | 75% | 1 | 9 | $5.000 | $44.586 |
| Legal | 4 | 0 | 12 | 4 | 5% | 0 | 0 | $10.000 | $0 |
| | | | | | | Total | 22 | | $65.911 |

**Uncertain Variables**
Cells F26:F32 contain the PsiTriangular distributions that model the estimated completion time (in weeks) for each potential PsiTriangular (a,c,b,...) PsiTriangular (a,c,b) is a distribution with lower bound a, upper bound b, and most likely value c so here Likely, Best, Worst Case.

| | | | |
|---|---|---|---|
| Number of Weeks to Completion: | 73 | Estimated Cost: | $376.396 |
| Months: | 18,2 | | |
| Average Duration (weeks): | 65,6 | Average Cost: | $364.247 |
| Probability that product will be finished within 65 weeks (15 mos): | 45,0% | Prob Cost <$300K: | 4,9% |
| Probability that product will be finished within 78 weeks (18 mos): | 97,2% | | |

Figure 7 Decision Preference Matrix

**No input in grey shaded cells**

## Decision Statement: "Identify therapeutic indication(s) with optimal fit to TwinBite7"

| number of criteria | | Development criteria | Must or Want criteria | Desired goal |
|---|---|---|---|---|
| 0 | | Clinical rational: Expression level of EPCAM on tumor cells higher tha | Must | meet criterium |
| 0 | | Existing clinical correlates to EPCAM: At least two studies showing po | Must | meet criterium |
| 0 | | Phase I in not more than one year from now | Must | meet criterium |
| 0 | | Budget must not exceed 1,5Mil € till end of Phase I | Must | meet criterium |
| 0 | | Budget must not exceed 50Mil € for whole clinical study program | Must | meet criterium |
| 0 | | | Must | meet criterium |
| 0 | | | Must | meet criterium |
| 1 | A | Clinical rational: Expression level of EPCAM on tumor cells as high as | Want | |
| 2 | B | Existing clinical correlates to EPCAM: more than two studies showing | Want | |
| 3 | C | Phase I as early as possible | Want | |
| 4 | D | Cost as low as possible till end of Phase I | Want | |
| 5 | E | Epidemiology: High incidence of disease | Want | |
| 6 | F | Low competition | Want | |
| 7 | G | High Pricing | Want | |
| 8 | H | Ideal combination partner for TwinByte with withoutout overlapping tox | Want | |
| 9 | I | Animal model for indication in place | Want | |
| 10 | J | Interest of potential partner already exists | Want | |
| 11 | K | High medical need (addressed by competitors but remains unsatisfact | Want | |
| 12 | L | Potential use as first line therapy | Want | |
| 13 | M | Surrogat parmaters available | Want | |
| 14 | N | Easy definable endpoint | Want | |

**compare criteria**

**Preference matrix**

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A | | | | | | | | | | | | |
| C | A | | | | | | | | | | | |
| C | D | A | | | | | | | | | | |
| E | E | E | A | | | | | | | | | |
| E | F | C | F | A | | | | | | | | |
| L | E | G | C | G | A | | | | | | | |
| H | H | H | H | C | H | A | | | | | | |
| H | I | F | E | I | C | I | A | | | | | |
| J | H | J | J | E | J | J | J | A | | | | |
| K | K | H | K | K | K | K | C | K | A | | | |
| K | J | I | L | G | F | E | D | C | L | K | | |
| M | K | J | M | H | M | F | E | D | C | M | A | |
| N | N | K | N | N | H | N | F | E | D | N | N | A |

| | | |
|---|---|---|
| number of "wish" criteria filled in automatically according to text input under "Development" column | 14 | |
| Sum of all possible deciscions: | 91 | |
| You have made | 91 | inputs, decisions respctively |
| there are still | 0 | decisons to make |
| 100% = number of decisions plus number of criteria (Default is "1" for ech criterion) | 105 | (this is: "Sum of all possible deciscions) plus "number of "wish" criteria") |

| Goals: | A | B | C | D | E | F | G | H | I | J | K | L | M |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of times (+1): | 13 | 1 | 10 | 5 | 11 | 7 | 4 | 11 | 5 | 9 | 12 | 4 | 5 |
| % weightning: | 12,38% | 0,95% | 9,52% | 4,76% | 10,48% | 6,67% | 3,81% | 10,48% | 4,76% | 8,57% | 11,43% | 3,81% | 4,76% |

If < or > 100% => wrong input or too many or too few inputs: **100,0%**

Figure 8 Comparisons of Alternatives

| Criteria | | ~~Alternative 1~~ ~~Colorectal CA~~ | | | Alternative 2 Ovarian CA | | | Alternative 3 Pancreatic CA | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Quanification | Properties | Yes / No | | Properties | Yes / No | | Properties | Yes / No | |
| Clinical rational: Expression level of EPCAM on tumor cells higher than on normal tissue | | 3 papers | Y | | 2 papers | Y | | 3 papers | Y | |
| Existing clinical correlates to EPCAM: At least two studies showing positive outcome | | 4 studies | Y | | 4 studies | Y | | 4 studies | Y | |
| Phase I in not more than one year from now | | 18 months | N | | 12 months | Y | | 6 months | Y | |
| Budget must not exceed 1,5Mil € till end of Phase I | | 1,2 mio | Y | | 1 mio | Y | | 1 mio | Y | |
| Budget must not exceed 50Mil € for whole clinical study program | | 2 Studies with 500ptn=> 100Mio. Estim. Cost | N | | ca 50 Mio for 1-2 pivotal PhaseII | Y | | ca 30 Mio for 1-2 pivotal PhaseII | Y | |
| 0 | | | | | | | | | | |
| 0 | | | | | | | | | | |
| | Weight | Properties | Evaluation | Weight x | Properties | Evaluation | Weight x Evaluation | Properties | Evaluation | Weight x Evaluation |
| Clinical rational: Expression level of EPCAM on tumor cells as high as possible | 0,13 | Very high expression level | ~~9~~ | ~~1,2~~ | High expression level | 7 | 0,9 | High expression level | 5 | 0,7 |
| Existing clinical correlates to EPCAM: more than two studies showing positive outcome | 0,01 | see Appendix | ~~7~~ | ~~0,1~~ | see Appendix | 10 | 0,1 | see Appendix | 4 | 0,0 |
| Phase I as early as possible | 0,10 | 18 months from now | ~~1~~ | ~~0,1~~ | 12 months from now | 7 | 0,7 | 6 moths from now | 10 | 1,0 |
| Cost as low as possible till end of Phase I | 0,04 | correlating to precli. Time cost plus phase I cost | ~~1~~ | ~~0,0~~ | correlating to precli. Time cost plus phase I cost | 7 | 0,3 | correlating to precli. Time cost plus phase I cost | 10 | 0,4 |
| Epidemiology: High incidence of disease | 0,10 | High incidence / prevalence | ~~10~~ | ~~1,0~~ | Low incidence / prevalence | 2 | 0,2 | Low incidence / prevalence | 1 | 0,1 |
| Low competition | 0,07 | many approved products on market | ~~2~~ | ~~0,1~~ | few approved products on market | 7 | 0,5 | 3 approved products on market | 9 | 0,6 |
| High Pricing | 0,04 | according to comp and med need | ~~3~~ | ~~0,1~~ | according to comp and med need | 6 | 0,2 | according to comp and med need | 8 | 0,3 |
| Ideal combination partner for TwinByte with withoutout overlapping tox and different MoA on tumor cells | 0,10 | according to compounds on market | ~~9~~ | ~~0,9~~ | according to compounds on market | 4 | 0,4 | Very good data for comi with gemcetabine | 9 | 0,9 |
| Animal model for indication in place | 0,05 | no data | ~~2~~ | ~~0,1~~ | some good data from animal mod | 6 | 0,3 | Xenograft mod in place | 9 | 0,4 |
| Interest of potential partner already exists | 0,09 | interst from company | ~~8~~ | ~~0,7~~ | no interest so far | 2 | 0,2 | no interest so far | 2 | 0,2 |
| High medical need (addressed by competitors but remains unsatisfactory) | 0,11 | | ~~5~~ | ~~0,6~~ | | 7 | 0,8 | | 10 | 1,1 |
| Potential use as first line therapy | 0,04 | related to number of approved compounds | ~~3~~ | ~~0,1~~ | related to number of approved compounds | 5 | 0,2 | related to number of approved compounds | 8 | 0,3 |
| Surrogat parmaters available | 0,05 | no data / min residual easease potentially | ~~2~~ | ~~0,1~~ | no data / min residual easease potentially | 2 | 0,1 | no data / min residual easease potentially | 2 | 0,1 |
| Easy definable endpoint | 0,08 | intermediate | ~~5~~ | ~~0,4~~ | intermediate | 5 | 0,4 | short survival => easy to follow up | 8 | 0,6 |
| | | | | ~~5,58~~ | | | 5,21 | | | 6,74 |

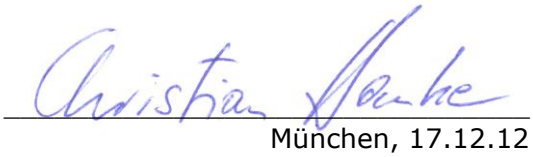
Table 12 Risk Assessment

| | Development criteria | | Risk scoring | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Alternative: | | | Alternative: | | |
| | | | | Ovarian CA | | | Pancreatic CA | | |
| | | | Assess adverse consequences/risks | P | S | Sum | P | S | Sum |
| **Must** | Clinical rational: Expression level of EPCAM on tumor cells higher than on normal tissue | | expression level could be lower than in vitro data / animal models / literature suggest | 2 | 3 | 6 | 1 | 3 | 3 |
| **Must** | Existing clinical correlates to EPCAM: At least two studies showing positive outcome | | | | | 0 | | | 0 |
| **Must** | Phase I in not more than one year from now | | due to unexpected bottlenecks need more time | 2 | 3 | 6 | 2 | 3 | 6 |
| **Must** | Budget must not exceed 1,5Mil € till end of Phase I | | Budget could be overrun | 2 | 2 | 4 | 2 | 2 | 4 |
| **Must** | Budget must not exceed 50Mil € for whole clinical study program | | Comp Authorities culd request more pts.; endpoint is only a surrogate or not "hard" enough | 2 | 3 | 6 | 1 | 3 | 3 |
| **Want** | Clinical rational: Expression level of EPCAM on tumor cells as high as possible | | | 2 | 2 | 4 | 1 | 3 | 3 |
| **Want** | Existing clinical correlates to EPCAM: more than two studies showing positive outcome | | | | | 0 | | | 0 |
| **Want** | Phase I as early as possible | | | | | 0 | | | 0 |
| **Want** | Cost as low as possible till end of Phase I | | | | | 0 | | | 0 |
| **Want** | Epidemiology: High incidence of disease | | Incidence could be too low to achieve ROI; could not find pat for study or becomes very expensive | 2 | 3 | 6 | 3 | 3 | 9 |
| **Want** | Low competition | | Till end of clinical program competition could be much higher; threat: mAB with similar | 3 | 3 | 9 | 3 | 3 | 9 |
| **Want** | High Pricing | | reimbursement policy could constrain ROI | 1 | 3 | 3 | 1 | 3 | 3 |
| **Want** | Ideal combination partner for TwinByte with withoutout overlapping tox and different MoA on tumor cells | | In a clinical setting it turn out that there is overapping tox & similar MoA | 2 | 2 | 4 | 2 | 2 | 4 |
| **Want** | Animal model for indication in place | | | | | 0 | | | 0 |
| | | | **Sum** | | | 48 | | | 44 |

Table 13 Risk Analysis of Alternatives

| Assess adverse consequences/risks | Preventive Measures | Contingency Measures |
|---|---|---|
| expression level could be lower than in vitro data / animal models / literature suggest | Refine animal models, use species that compares best to human; do extensive survey of literature (and patents) | Eventually stop program to limit money at risk sunk money; try share deal of TwinByte 333 |
| due to unexpected burdens / bottlenecks need more time | Try to plan stringently (gant charts, milestone tracking, balanced score card...); tied reporting to the board; implement program manager who is backed by the board; try to foresee the risks by constantely check "target-performance" comparison etc. | provide the time which is needed if possible |
| Budget could be overrun | same as above | CEO's main and "noblest" task: asure that there will be a fresh financing; re allocate / shift budget from other projects |
| Comp Authorities could request more pts.; endpoint is only a surrogate or not "hard" enough | provide excellent briefing package - clarify with scientific adivice;stand up / defend your position; be in contact with comp authorities continously; try to avoid surrogates | if surrogates can not be avoided they must b validated by a study; initiate validation study in advance of the clinical program |
| Incidence could be too low to achieve ROI; could not find pat for study or becomes very expensive | check incidence /prevalence ; calculate DCF | |
| Till end of clinical program competition could be much higher; threat: mAB with similar MoA | etc | etc |
| reimbursement policy could constrain ROI | etc | etc |
| In a clinical setting it turn out that there is overapping tox & similar MoA | etc | etc |
| | | |

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.



München, 17.12.12
Dr. Christian Hanke