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Defining Therapeutic Area Strategies

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Abstract

Ever increasing expenses in global R&D and a stagnating R&D output have led to a disillusioning net balance that forces pharmaceutical companies to rethink their strategy. Defining therapeutic area (TA) strategies today has little to do with “company-heritage”. Already existing resources or established expertise no longer deduce the future therapeutic area strategy. Instead, companies need to consider commercialization opportunities and the competitive situation.

As a consequence, we have seen that many pharmaceutical companies radically shift their R&D activities – a decision that will determine the future success of a company to a high extend. Defining a therapeutic area strategy, therefore, has to follow a systematic funnel identifying attractive segments from a company's perspective. A multi-stage process is necessary to deduce the new TA strategy.

Such approach will be successful when leveraging all available sources of knowledge within a company and making best use of additional data and external expert support.

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Companies need to rethink their Therapeutic Area Strategy

Pharmaceutical companies increasingly feel the pressure of having to adjust their R&D focus. Over recent years companies have left well-established R&D areas, have given up on the experience and know-how they have built over decades and entered new therapeutic areas. Why is that so?

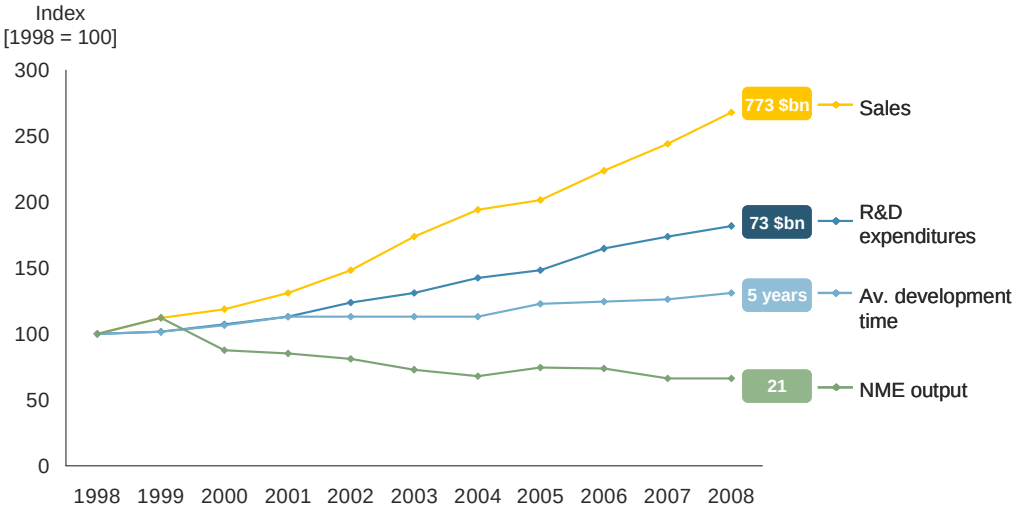
If you have followed the press carefully during the last months, you will have noticed that Pfizer gave up large parts of its Cardiovascular diseases research, that Merck Serono withdrew from Diabetes research, that Bayer Schering will stop its own research activities in the field of Bacterial Infections and that Roche handed over its Antibiotics and Dermatology research to Basilea, to name just a few examples. (see Abb. 1)

Abb. 1
Announcements of companies to leave certain areas in R&D

1) USA today (2009) 2) Pressrelease Basilea (2000) 3) Chemie.de (2006) 4) Pressrelease Merck-Serono (2007) 5) Press release Merck-Serono (2010) 6) Pharmanews.eu (2008) 7) Euro Pharma Today (2010)
Source: CEPTON Strategies

There are many reasons for this development! Despite ever increasing expenses in global R&D the output in terms of new medical entities (NME) has been stagnating, even decreasing, in recent years (see fig. 2) – a disillusioning net balance that forces pharmaceutical companies to rethink their strategy.

Fig. 2
Relation of revenues, R&D investment and output of NMEs in the global pharmaceuticals industry



Source: CEPTON Strategies

When looking at R&D outputs in detail, you will see that years 2004 to 2008 saw a continuous increase in the number of Phase 1 projects whereas the number of Phase 3 projects, and even worse, the projects that reached marketing authorization, decreased by approximately 40%. To put it in simple words, during the last ten years, a considerably higher input, in terms of value and resources, has generated a considerably lower output. To make the situation worse, there also has been a relative increase in R&D costs – per patient – due to the growing number of regulatory requirements and procedures.
Taking all terminated projects into account (projects that do not reach official marketing authorization) that a company had to go through to come up with the NME, the overall costs sum up to one billion USD.

But significant changes did not only occur with regard to R&D. Companies are also forced to handle significant changes with regard to the market, that is the market commercialization of a product.

Market access limitations lead to a rethinking of the future marketing strategy and achievable price levels. Real cost--benefit analyses are necessary in order to establish the required data basis that proves that the innovation does not simply lead to higher cost of the therapy but has a significant positive cost-benefit ratio. Things become even more complicated when remembering that there are no established global standards for quantifying the benefit of innovations. Today companies have to deal with different cost-benefit standards from different regulatory authorities.

As a consequence, major pharmaceutical companies are often forced to shift the focus of their research & development activities. An industry-wide analysis of pipeline candidates by therapy area and indication demonstrates that even big, globally active pharmaceutical companies increasingly focus on niche markets. Molecular targeted therapies are spearheading a paradigm shift in oncology. Stratified strategies lead to products that are no more suitable for all patients, but can only be applied to a predefined part of the population. Pharmaceutical companies favor therapeutic areas that do not focus on the huge number of general practitioners, but target niche markets and medical specialist areas. All in all, the global pharmaceutical industry is withdrawing from traditional R&D areas like Metabolic Diseases, Cardiovascular Diseases, and Diabetes Mellitus, whereas niches like the Central Nervous System, Orthopedics or Endocrinology become increasingly attractive.

Today the strategy of research-based companies cannot be solely based on the question of existing resources or of their established expertise in a particular field, instead, a given strategy has to include possible future commercialization options and the competitive intensity in the considered therapeutic area.

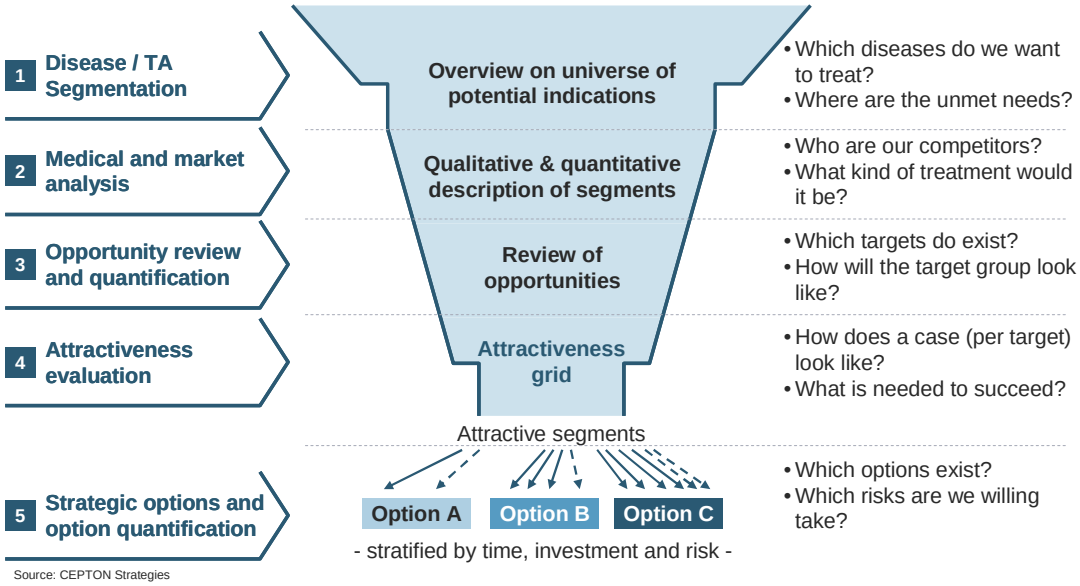
Defining TA strategies today has little to do with “company-heritage”. Already existing resources or established expertise in a therapeutic area no longer deduce the future therapeutic area (TA) strategy of a company. Instead, companies need to consider future commercialization opportunities and the competitive situation.

How to deduce a Therapeutic Area Strategy

We have seen that many pharmaceutical companies radically question and shift their R&D activities. Companies do not only withdraw from traditional research areas, they even break with their roots and explore new, promising frontiers of research.

Defining a TA strategy today has to follow a systematic funnel to identify attractive segments from a company's perspective. As illustrated by the figure below, a multi-stage process is necessary to deduce the new TA strategy of a pharmaceutical company. Targets with high potential are identified by systematic segmentation, a detailed analysis of the “*unmet medical needs”* and the market environment.

Abb. 3
A five step-approach is required to define a Therapeutic Area (TA) Strategy



Source: CEPTON Strategies

Such an approach can only be implemented if synergies between all available sources of knowledge and resources within a company are reaped. But even when using all in-house sources available, establishing a new TA strategy will depend on making additional data, knowledge and external expert know-how available.

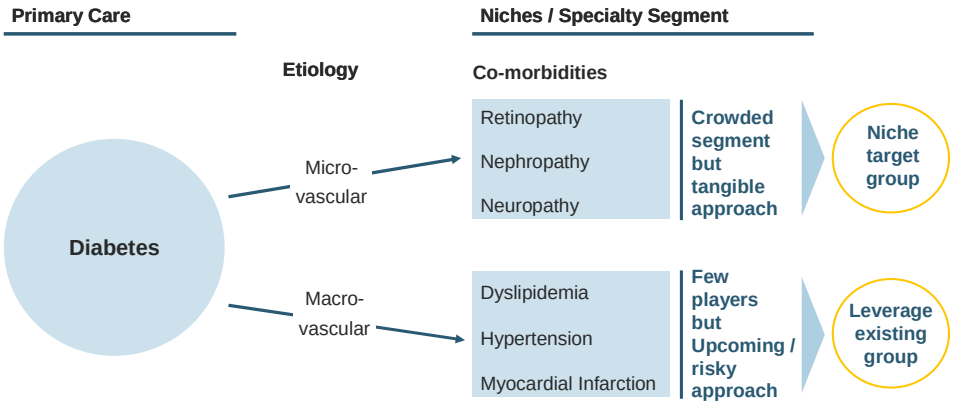
Beyond a given fundamental attractiveness and feasibility of certain R&D projects, the main question will be whether potential targets are available. Especially since pharmaceutical companies today derive more than half of their new business from products they did not develop themselves.

In order to assess the attractiveness of a strategic option, companies today do not only have to consider the scientific feasibility of a project, but also the attainable price-level, based on comprehensive cost-benefit analyses, and future commercialization possibilities. Recently companies started to focus on specialist products in Oncology, Neurology and other niches – one reason being the higher price-levels that can be achieved – and this way avoid the dilemma of increasing market access hurdles and decreasing price-levels in the traditional R&D areas. However, this development clearly shows that it cannot be an objective of the industry or a consequence of cost containment measures, to only focus on R&D activities for rare diseases and to start neglecting widespread diseases, just because these are commercially less attractive. Deducing a new therapeutic area strategy is influenced by diverse aspects. For this reason new strategy options virtually have to run through a filter that will answer all critical questions in five predefined steps.

Segmentation

As a first step, potentially interesting therapeutic segments (for example degenerative diseases of the Central Nervous System or Endocrine Diseases) have to be selected and brought into a systematic segmentation. An in-depth understanding of the existing indications, clinical endpoints and notably of the "*unmet medical need*" within the therapeutic area needs to be developed. Within a segment, sub-indications can be identified, for which respective therapeutic pathways have to be investigated. In some cases it can make sense to identify complications of existing therapies or co-morbidities. Co-morbidities may represent a way out of crowded primary care therapies. Consider, for example, the treatment of a Type 2 Diabetes Mellitus patient: There is no high unmet medical need, nor will the treatment be commercially attractive. By contrast, the complications of Diabetes Mellitus, such as Nephropathy, Neuropathy, Retinopathy and so on, can be highly attractive not only from a medical but also from a commercial point of view (see fig. 4). Of course, at this stage you already have to ask yourself whether an identified unmet medical need is a fit to your company's preclinical and clinical R&D expertise. This way more than 2/3 of potential therapeutic areas are usually excluded in the first step of the pre-defined filter.

Fig. 4
Distinction of primary disease and secondary complications may reveal attractive areas for development



Source: CEPTON Strategies

Medical and market analyses

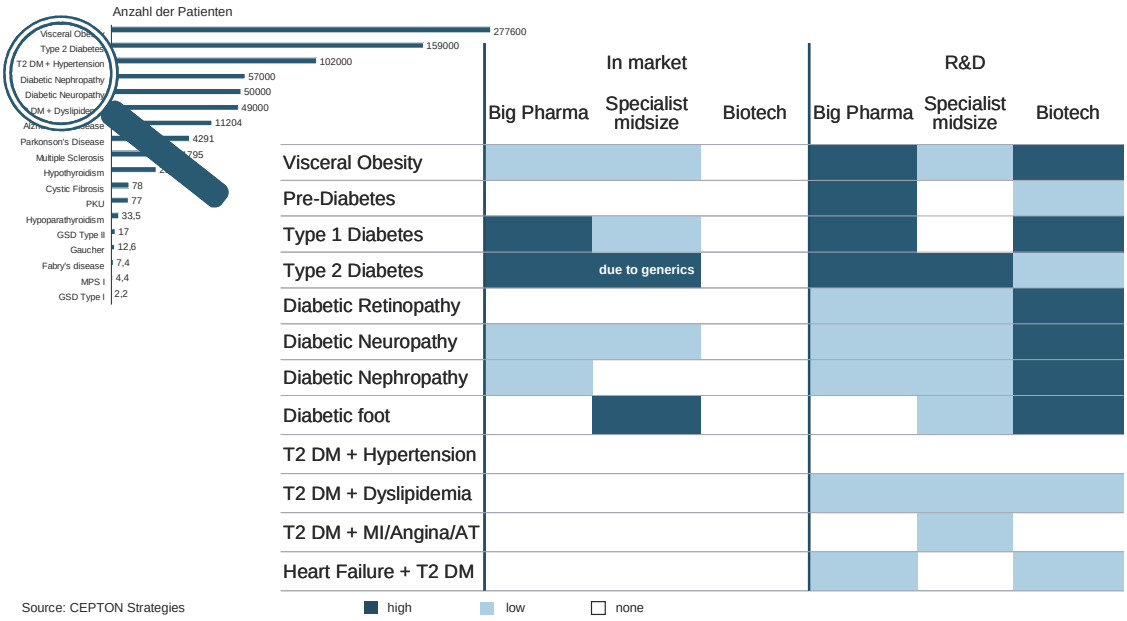
As a consequence of setting the R&D focus of a company on certain diseases or indications, all R&D resources of the company are aligned to the chosen focus. Before such a decision can be made – a decision that affects the work of hundreds of employees over many, many years – the scientific and economic potential of an indication has to be analyzed. As soon as the scope of segments is defined within the context of the segmentation process, a detailed medical and market analysis has to be elaborated. Companies need to analyze the epidemiology in detail, meaning companies have to ask themselves what type of patients and how many patients are affected by the indication, what the diagnosis rate is, what regional differences exist and how these aspects will change within the next 30 to 40 years. This time horizon is important since a new product will not be launched until ten years after the decision on the R&D focus is made.

Besides analyzing the epidemiology it is also necessary to ask, whether and what kind of therapeutic approaches already exist. This particularly concerns early targets that promise to develop into lead compounds. For this purpose literature researches, pertinent databases (e.g. IDDB3) and direct contacts to opinion leaders and universities are used to determine whether any scientists and researchers around the world have already been working on given targets. Often these promising, early targets are not found in big pharmaceutical companies, but are explored by scientists in small companies or universities. It takes the effort of many functions within a company and external experts, to sufficiently analyze the potential of early targets (phase 0 and before). Of course, even in such an early stage, one has to consider whether an in-licensing or cooperation agreement can be attained for the target.

On top of the purely scientific analysis of the potential, companies have to question at a very early stage, what a potential commercialization would look like. What target group should be addressed? What internal structures are needed for a successful commercialization? What regional differences have to be considered? What does the future price-level of the targeted therapy look like?
We are definitely not giving away too much when saying that today a couple of research projects – although promising - are not further explored due to the low price-level of the indication. With research projects competing for the limited internal resources of a company, these projects simply have no chance.

A comprehensive evaluation of attractiveness includes an analysis of the competitive environment. Is the market already occupied by big players – having products on the market and innovations in their pipelines – or is it mostly free of global competition? Such a competitive analysis often identifies niches that are interesting for a company's own R&D activities.

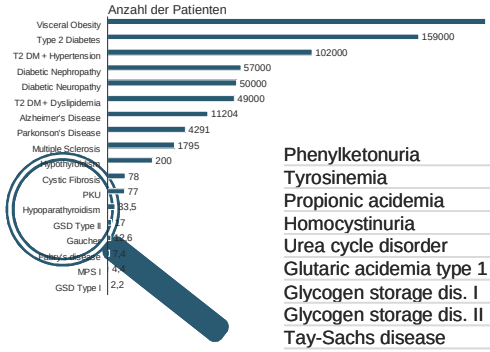
Fig. 5
Competitive analysis of marketed portfolios and pipelines will identify niches to focus on



Source: CEPTON Strategies

At the same time, this step in finding the right strategy displays the direction other companies have chosen to take. The analysis of the competitive environment, the number of marketing authorization applications per indication and the R&D focus of main competitors will show, where to set one's own focus, in order to have a chance of being “first to market” and not be competing with big players (see fig. 6).

Fig. 6
The future competitive landscape can be anticipated by looking into the pipelines



	Pfizer	Merck Serono	UCB	Shire	Novo Nordisk	Genzyme	Zymenex	Protalix	Galaczym	Crucell	Biomarin	Altus	Amicus	Aimspro	Actelion	Total[2]
Phenylketonuria		2									2	1				3
Tyrosinemia																
Propionic acidemia																
Homocystinuria																
Urea cycle disorder																
Glutaric acidemia type 1																
Glycogen storage dis. I																
Glycogen storage dis. II						1							1			2
Tay-Sachs disease	1		1			1										2
Niemann-Pick disease	1		1			2									1	4
Farber disease																
Fabry’s disease								1					1			2
Gaucher’s disease				1	1	2				1			1			5
Metachromatic leukodystrophy				1			1									2
Krabbe’s disease									1					1		2
Batten’s disease																
Lesch-Nyhan syndrome																
MPS type III				1												1

Source: CEPTON Strategies 1) Review time autumn 2008 2) Refers to number of projects in each segment and is therefore lower than the number of active companies

This method also reveals how even multinational companies that have been focusing on widespread diseases like Diabetes, Cardiac Insufficiency and Hypertension or Bacterial Infections now shift to therapeutic niches (see fig. 7).

Fig. 7
Recent approvals by FDA and EMEA indicate a paradigm change

FDA approvals 2009 (Specialist areas blue)

Drug name	Indication	Company
Temodar	Brain cancer	Schering
Afinitor	Renal Cell Carcinoma	Novartis
Coartem	Malaria	Novartis
Tyzeka	Hepatitis B	Novartis
Exforge HCT	High blood pressure	Novartis
Lamictal	Epilepsy	SmithKline Beec.
Prevacid	Duodenal Ulcer	Novartis
Adcirca	Pulmonary Art. Hypertension	Eli Lilly
Lamictal XR	Epilepsy (partial seizures)	SmithKline Beec.
Ilaris	Cryopyrin-As. Periodic Syn.	Novartis Pharms
Multaq	Atrial fibrillation (AFib)	Sanofi-Aventis
Effient	Acute Coronary Cyndrome	Eli Lilly
Invega Sust.[2]	Schizophrenia	J&J
Arzerra	Lymphocytic Leukemia	Glaxo GRD
Onglyza	Diabetes	BMS
Extavia	Multiple Sclerosis	Novartis Pharms
Valcyte	Herpes	Roche
Valturna	High blood pressure	Novartis
Welchol	Diabetes	Daiichi-Sankyo
Twynsta	Hypertension	Boehringer-Ingelh.
Votrient	Renal cell carcinoma	GSK
Revatio	Pulmonary Hypertension	Pfizer
Zyprexa Relpr.	Schizophrenia	Eli Lilly

Orphan registrations EMEA 2007-2010[1]

Drug name (active subst.)	Indication (TA)	Company	Year of approv.
Arzerra (Ofatumumab)	Leukemia, Lymphocytic, Chronic, B-Cell	GSK	2010
Revolade (eltrombopag)	Purpura, Thrombocytopenic, Idiopathic	GSK	2010
Ilaris (canakinumab)	Cryopyrin-associated Periodic Syndromes	Novartis	2009
Kuvan (Sapropterin dihydrochloride)	Hyperphenylalaninemia (Endocrinology / Metabolism)	Merck KGaA	2008
Volibris (Ambrisentan)	Pulmonary Arterial Hypertension and Chronic thromboembolic pulmonary hypertension (Cardiovascular / Resp.)	GSK	2008
Elaprase (Iduronate-2-sulfatase)	Mucopolysaccharidosis, type II, Hunter syndr. (Endocrinology / Metabolism)	Shire	2007
Inovelon (Rufinamide)	Lennox-Gastaut syndrome (Nervous system)	Eisai	2007

Source: CEPTON Strategies 1) examples – non exclusive list 2) Invega Sustenna 3) Zyprexa Relprevv

Opportunity review and quantification

As soon as the scope of the future R&D activities has been narrowed down as described above, the next step will be a detailed opportunity review and quantification of individual targets.
As shown in figure 8, each mode of action has to be identified and described, the future price and target group size (therapies per year) has to be determined and different in-licensing options, as well as research activities required for the remaining clinical stages have to be discussed.

Abb. 8
The pipeline assessment reveals opportunities, the remaining time to market and competitive intensity

	Pre	I	II	III	Reg	Companies	Status
Regulation of GI signals	16	5	1			Nobex, Amylin, PPL Therap., Alizyme, Cytosm, Nastech, Emisphere, IC Innovat, [...] Sappire, Pfizer, J&J, Lilly, NovoNordisk	R
Regulation of energy expenditure	22	1	4			Kyorin, Sanwai, Molecular Design Intl., Karo Bio, ENdochem, Quartx, Adipo-genix, Biovitrum, Johns Hopkins, Aurigene, Forbes, Fas-gen [...] Biotech, Aegis, Amylin, Turalik, Ligand, Pfizer, Lilly, GSK	R
Peripheral and hepatic insulin resistance	9	1				CrystalGeno., Kadmus, Kalypsys, Perlecan, Dr. Reddys, Adipogenix, NovoNordisk, GSK, Servier	R
Carbohydrates absorption/elimination	1		1			Ceptyr, Kissei	R
Growth hormone and derivatives	4		1			Atrix, Tulane Univ., Metabolic, BresaGen, Pr.F.NG., Abbott	R+ (D)
Gene based therapy	8					Autogen, Develogen, Azign, Devgen, Mirus, Genfit, Myriad, Xenon	
Regulation of lipid digestion/absorption	9	1	1		2	Reductogen-Ximed, Strathclyde, Alizyme, Genzyme, Morshita, Japan.Net.Inst. of Health&Nutr., Phytomedics, Millenium, Roche, GSK, Takeda	

	Clinical or Preclinical PoC	Discovery Research	Expertise / Project ideas
Internal Opportunities/ Synergies	• Growth hormones		• Previous serotonin research • Increase of energy consumption through modified thyroid hormone action (e.g. receptor beta agonist)

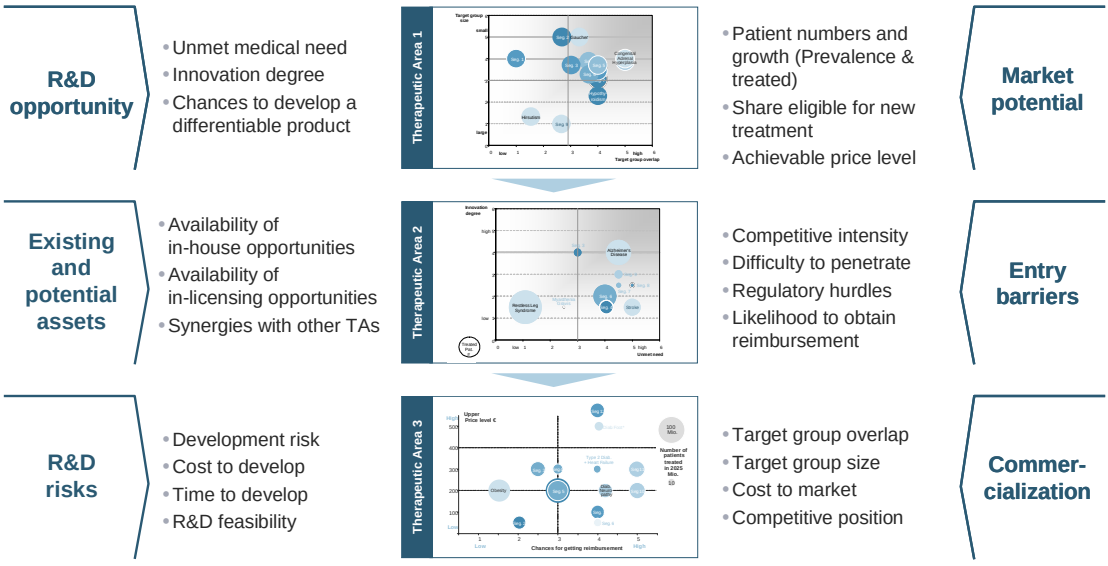
Source: CEPTON Strategies

The required financial investments and the time it takes to complete the clinical development of the identified targets, expected patent protection time and estimated peak sales must be defined. The last step of deducing a new TA strategy cannot be done without compiling the information described.

Attractiveness evaluation

The attractiveness evaluation consists of a comparative analysis, visualized in attractiveness matrices. Segments and targets are thereby evaluated with regard to their attractiveness along several criteria.

Fig. 9:
Various criteria have to be combined to allow for a sound attractiveness evaluation



Source: CEPTON Strategies

These criteria include the unmet medical needs, the number of available targets within an indication and the R&D risk, but also commercial aspects such as number of treated patients, achievable price level, market access hurdles and market commercialization requirements. Combining the different attractiveness criteria will identify and visualize the segments on which to base the corporate strategy.

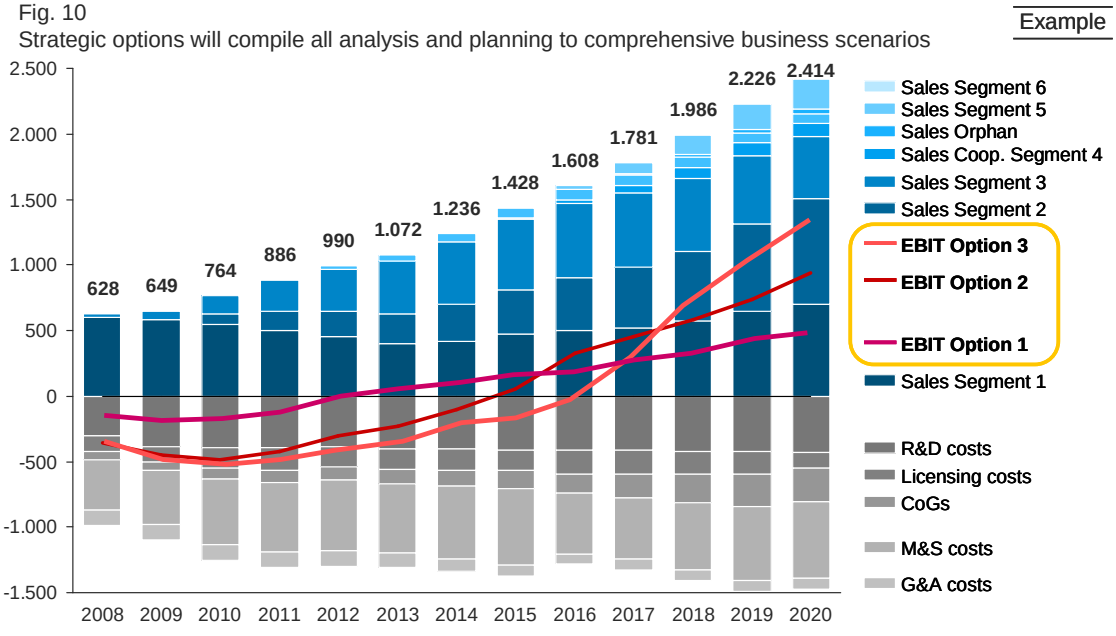
Finally, strategic options have to be developed that quantify the future of the company financially. This means, comprehensive strategic options are built, based on the identified targets, and quantified in form of business cases. The business cases need to describe in detail what in-licensing cost and royalties have to be considered, how high the preclinical and clinical R&D investments will be, what financial resources will be required for market commercialization, what co-marketing or co-promotion agreements will be made and how these will affect the cost structure of the strategic option and last but not least, how the therapy price will develop over the next decades, following market entry.

Strategic options and option quantification

In order to describe the possible strategic options, criteria have to be defined that allow to differentiate the various options. Such criteria include “total investment required“, “time to break even“, “revenues at risk“, “percentage of licensing“ and of course estimated “top line” sales (will be employed?). The reason for this methodological process is that companies have to decide between different strategic options. The chosen strategic option will determine the company’s scope, within which future decisions can be made.

In addition to the strategic options, scenarios that depict non-controllable, external influences have to be developed. These scenarios serve as a foundation for future decisions. They allow for the simulation of the statistical risk (success rates in dependence of clinical phases and milestones achieved), as well as the competitors’ behavior, market developments and price variability (see fig. 10).

Fig. 10
Strategic options will compile all analysis and planning to comprehensive business scenarios



Source: CEPTON Strategies

It is evident that the definition of “strategic options for research and development in pharmaceutical companies” involves juggling quite a few unknown variables. As unpredictable as pre-clinical and clinical development is, it is highly important, that all variables and framework conditions applied in the development of a business case should be described in detail. A rolling R&D forecast and R&D controlling over a period of 10 years and longer, that allows a company to make a sound decision on continuing or terminating a project, will only be possible, if this description was taken seriously.

Changes in only 2 or 3 of the framework conditions within the overall concept of variables, may lead to a completely new evaluation of the strategic option; they may change the setting of the strategic agenda completely and lead to a different allocation of the financial resources of the company. This shows the significance of re-evaluating the strategic option. And this re-evaluation is possible only if based on sound, continuous R&D controlling.

When analyzing the activities of research-based companies over the last years, you will realize that, as a consequence of the described process, some therapeutic areas have become less attractive while for other indications the opposite was the case. Research-based pharmaceutical companies are more and more heading towards therapeutic areas that are covered by specialized physicians, consist of small target groups (physicians or patients) and have a high price-level. Companies try to avoid therapeutic areas that are highly competitive and prefer a local scope over a global scope. In addition, chronic diseases with a high unmet medical need will always be preferred to short-term therapies (see fig. 11).

Fig. 11
Typical attractiveness patterns have been re-shuffling R&D investments recently

Criteria to leave	Criteria to enter/stay
GP dominated segment	Specialist focus
Large target groups	Small target groups
Low prospective prices → small molecules	High prospective prices → biologicals
Dominated by big Pharma	Relatively low competition
Global scope (per se)	Regional approach
Short therapies	Life-long (maintenance) therapies
Little value added	High unmet need
Difficult market access (total cost-benefit)	Positive total cost-benefit
To be developed “on your own”	Development alliances possible
Developed in-house only	“license as late as possible”

Source: CEPTON Strategies

Companies today also have to consider (and include the corresponding parameters in their clinical testing), if only in phase 0, whether a project will turn into an innovative therapy with a positive cost-benefit ratio. Only if this is the case, it will make sense to start a multi-million euro project.

Fig. 12
Announcements by Big-Pharma to enter certain therapeutic areas

Roche	Oncology, Virology, Inflammation, CNS, Metabolic Diseases
genzyme	Focuses especially on Orphan Diseases
Pfizer	Trend towards specialty pharma segments, especially Oncology R&D activities split into two separate units
Shire	Human Genetic Therapy Division focuses on Orphan Diseases
MERCK SERONO	CNS, Oncology, AIID, Fertility
sanofi aventis	Multiple Sclerosis
NOVARTIS	Multiple Sclerosis
gsk GlaxoSmithKline	Duchenne’s disease (acquisition of Prosensa)

Source: CEPTON Strategies

If you look at the R&D focus of global research-based pharmaceutical companies, you will realize that certain therapeutic areas – that follow the above mentioned criteria – have become very popular. This is true for Oncology and especially for Virology, Inflammatory Diseases and Degenerative Neurological Diseases, just to mention a few. Figure 12 shows that pharmaceutical companies have now been setting their focus on these therapeutic areas.

On the other hand it is pretty disillusioning to see how the in-licensing of targets that were once initiated, do not seem very promising. If you take a close look at the R&D projects of the last years, you will realize that due to the growing in-licensing activities of the global pharmaceutical industry, the in-licensed phase 1 and 2 projects have increased considerably, as compared with self-initiated projects. By contrast, marketing authorizations during the same period were mainly granted for self-initiated projects and much less for in-licensed projects.

More than ever, pharmaceutical companies will have to shift their TA strategy. In addition to the described key attractiveness factors of a proposed R&D focus and commercialization options, companies will have to consider the opportunities in the field of personalized medicine. Regardless of the different therapeutic areas, personalized medicine offers new therapeutic options, like stratified medicine, vaccination and gene therapy. These options demand new, fundamental decisions.

About CEPTON

CEPTON, a globally acting strategy consulting firm, has its roots in one of the most renowned consulting firms globally. Our company was founded to provide a new consulting approach and advice to clients who are seeking solutions for their strategic questions. We believe in small teams of senior executives with many years of experience in strategic issues and operative management gained hands-on in the industry or major consulting firms.
CEPTON relies on the in-depth knowledge of a specific sector of activity as its mainstay. It is not generic methods but knowledge matured over the years in a given national and international industry environment that will generate success.
Our services are built on partnership with our clients and rely on the quality of our executives who are time-tested in finding customized solutions together with our clients rather than for them. We offer experts to work as interim managers of our clients' companies, if desired, where they take an active responsible part in driving the implementation in a timely and effective manner.

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