

# Big Pharma at the Crossroads

Recent strategic moves of globally acting pharmaceutical companies

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## Abstract

Strategies which might have been successful for Big Pharma in the past no longer have the desired impact in the ever-changing environment of the future.

Big Pharma is standing at the crossroads, feeling the urge to rethink their strategy. Biosimilars have entered the spot-light of innovative pharmaceutical companies. The regional focus is starting to shift away from China to second-tier emerging pharmaceutical markets and diversification has come to its limits and companies are starting to re-focus. The growing impact of payors and regulatory bodies has not only influenced the overall approach to market access, but also R&D decisions and business models. In most pharmaceutical markets risk sharing contracts have been established, in the light of market access tactics. Big Pharma is re-designing R&D, building global co-operations and networks and targeting more specialized therapeutic areas, with fewer patient numbers. Innovation for Big Pharma is no longer limited to drugs, but includes diagnostic, patient monitoring and digital health solutions. Big Pharma is undergoing a process of change. Still many changes are yet to come.

## Zusammenfassung

### Big Pharma am Scheideweg – Die strategische Neuausrichtung globaler Pharmaunternehmen

Das Umfeld großer Pharmakonzerne, auch Big Pharma genannt, unterliegt ständigen und massiven Veränderungen. Strategien, die bisher erfolgreich waren, werden in der Zukunft nicht mehr zum gewünschten Effekt führen.

Big Pharma steht damit am Scheideweg und muss Bewährtes überdenken. Biosimilars sind in den Fokus forschender Pharmaunternehmen gerückt. Der Schwerpunkt internationaler Strategien bewegt sich langsam von China weg und richtet sich auf die zweite Riege der pharmazeutischen Entwicklungsländer. Die Diversifikation hat ihre Grenzen erreicht und Big Pharma setzt wieder auf Fokussierung. Der wachsende Einfluss von Kassen und gesundheitspolitischen Organen hat nicht nur die Herangehensweise an Market Access, sondern auch R&D Strategien und Business Modelle verändert. Risk Sharing Verträge finden sich in allen Märkten, teils als reine Market Access Taktik. Big Pharma gestaltet R&D neu, baut globale Kooperationen und Netzwerke auf und zielt auf deutliche kleinere Patientenpopulationen. Innovationen beschränken sich nicht mehr nur auf Therapien; inzwischen stehen innovative Ansätze in Diagnostik und Patientmanagement bis hin zu Digital Health im Fokus. Big Pharma richtet sich momentan strategisch neu aus. Doch in den kommenden Jahren wird es noch viel Veränderung geben.

<sup>1)</sup> The views expressed in this article are the views and opinions of the authors, based on independent research and publicly available material, and do not reflect nor represent the views of any company or organization affiliated with the authors.

**Big Pharma rethinking strategy**

On average, pharma and biotech stocks have shown good performance in 2013, however, most of Big Pharma's stock price development in 2013 lagged behind the S&P 500 and Dax average.

The impact of payors and regulatory bodies continues to grow, influencing not only market access activities, but R&D decisions and business models. Diversification has seen first limits and big players like Abbott, Pfizer and BMS have started to re-focus. Biosimilars and over-the-counter (OTC) drugs have re-entered the spotlight. Regional focus is partly moving on from China to "second-tier" emerging markets like South-East Asia, Iran, Pakistan and Africa. A decrease in total number of deals and a focus on fewer therapeutic areas, such as oncology, anti-rheumatics and neurology can be seen. In light of increasing complexity and cost in R&D, the R&D paradigm seems to be changing, with more cooperation and less blockbuster products.

Adapting strategies, however, is not limited to R&D. Recent moves of Big Pharma affected their behaviour on mergers and acquisitions, causing a more focused look on the portfolio and more courageous steps into emerging markets and digital solutions.

**Responding to market dynamics and refocusing the portfolio**

Market dynamics are changing, requiring a refocus of products and therapeutic area coverage. This is obvious when looking at sales growth per therapeutic area.<sup>2)</sup> As shown in Fig. 1, today only a few therapeutic areas drive industry top line growth. Oncology, multiple sclerosis, rheu-

<sup>2)</sup> Evaluate Pharma World Preview 2013 / Cepton Research.

matoid arthritis, and anti-virals have moved into the spotlight. Diabetes remains a growing therapeutic area. Multiple sclerosis had the highest growth rate over the last year. Diabetes and rheumatoid arthritis are growing and are already one of the largest segments today. Anti-virals increased growth from 5% to 8% compared to recent years. Former flagships of therapeutic growth, such as hypertension, hyperlipidemia and pulmonology, show negative growth, forcing pharmaceutical companies to adapt portfolios.

Comparing the growth of global pharmaceutical markets by their development of per capita spending for medicines, it can be observed that former focus areas in emerging markets, such as China and India, are now developing at the same speed

as other developed pharma markets, such as France (with +2% per capita projected growth between 2012–2016)<sup>3)</sup>. Big Pharma's consideration of emerging markets changes as former rising stars begin to decline. While countries like South Korea, with a predicted increase of more than 10% spending per capita on medicines between 2012–2016, stand out, the "second-tier" emerging markets, including South-East Asia, Iran, Pakistan and Africa are shifting into Big Pharma's view.

OTC, for some pharmaceutical companies like Novartis or Sanofi, has always been a focus area and part of a global strategy. For Novartis, there is a clear decision to boost their OTC portfolio and broaden product range beyond cough, cold, pain and even the possibility to acquire MSD's

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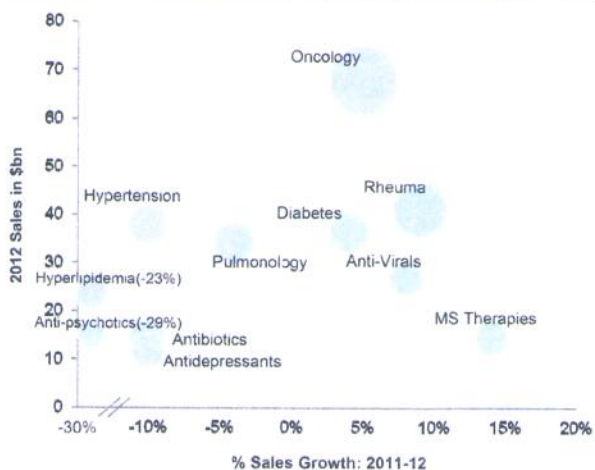
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<sup>3)</sup> US Census Database / OECD / Cepton Research.

**Figure 1**



*Sales and sales growth per therapeutic area between 2011 and 2012 (Source: Evaluate Pharma World Preview 2013 / Cepton Research).*

(Merck Sharp & Dohme) OTC portfolio – an opportunity that would represent approximately 5 bn US-dollars, as recently noted by some analysts<sup>4</sup>. Other pharmaceutical companies use OTC as a targeted tool to get “a foot in the door” of certain emerging markets. For Bayer, OTC products contribute to 45 % of its total Russian business and Pfizer acquired Poland’s big OTC player, Polocard, to establish a stronger position in the Central and Eastern Europe (CEE) market.

### Capitalizing on biotech and biosimilars

The pharmaceutical market will be increasingly dominated by biologicals. As shown in Fig. 2, the share of biotechnological products is projected to double within four years, representing 25 % of all prescription and OTC sales worldwide. The dominance of biotechnology is even more obvious when looking at the top 100 Pharmaceutical products in sales; by

<sup>4</sup> Bloomberg 2013 / Reuters 2013.

2018 half of these sales are projected to stem from biotechnology.

Today, more than 60 % of global “biotech” revenues are generated in only three therapeutic areas: oncology, diabetes and rheumatoid arthritis (Fig. 3). With leading “biotech” companies mostly based outside Europe, in-licencing deals in recent years

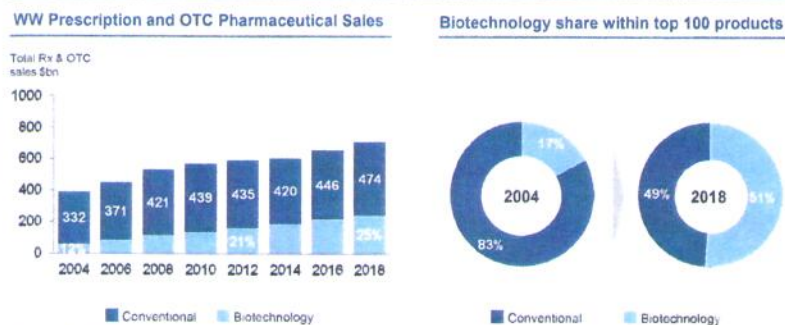
have focussed on a few rising stars in the biotech arena. Some examples include: Alexion, that will most likely triple their revenues to 3.7 bn US-dollars by 2018; Regeneron, who developed Eylea®/Zaltrap® in cooperation with Bayer and Sanofi for the treatment of ophthalmologic indications and cancer; Onyx Pharmaceuticals, now part of Amgen, that will most likely exceed revenues of 1.5 bn US-dollars by 2018; and BioMarin Pharmaceuticals. These companies are fuelling tomorrow’s innovative pipelines.

Regardless of geographic origin, the overall structure and size of pharma deals has lessened over the

past year. After years of huge deals, there is a trend toward smaller, more targeted acquisitions and asset swaps, such as the recent deal between GSK and Novartis. Two exceptions to this trend are the acquisition of Forest Labs by the former generics player Actavis for 25 bn US-dollars earlier this year, Amgen’s acquisition of biotech player Onyx and the acquisition of Sigma-Aldrich by the German-based Merck KGaA.

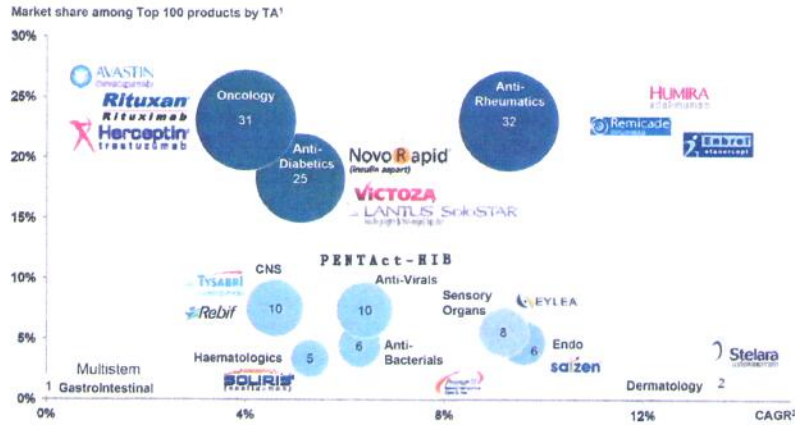
The global picture of Big Pharma deals today is driven by fewer and smaller acquisitions and more partnerships, aiming to strengthen the position in identified growth areas, such as oncology, HIV and central nervous system (CNS). Moreover, after many years of diversification, pharmaceutical companies are putting the “focus” on core competencies and high margin segments again, showing a willingness to de-invest and spin-off lower margin or non-focus businesses. Examples of these types of strategic decisions include GlaxoSmithKline’s (GSK) decision to sell off nutritional drink brands to Suntory Beverage & Food for 2.1 bn US-dollars or to give away formerly big brands such as Fraxiparine to Aspen Pharmaceuticals. Aspen in contrast, historically strong in South-Africa and in the generics market, buys into the global branded business. Bristol-Myers Squibb selling its stake in the diabetes cooperation with AstraZeneca for 4.3 bn US-dollars is another example of how Big

**Figure 2**



*Share of biologics on world wide pharma sales and top 100 products (Source: Cepton Research / Evaluate Pharma World Preview 2013).*

Figure 3



<sup>1)</sup> Based on Top 100 products <sup>2)</sup> CAGR (2012-2018)  
Outlook biotechnology market 2018 [bn US-dollars] (Source: Cepton Research / Evaluate Pharma World Preview 2013).

Pharma is moving away from the target group of general practitioners.

The biggest factor on overall portfolio strategies will likely result from the upcoming patent expirations of blockbuster biologicals. More than 40 patents on biologicals have expired by 2018, including huge biological products, such as Lantus<sup>®</sup>, Rituxan<sup>®</sup> and Remicade<sup>®</sup>. Just within the next three years, products with total revenues of 32 bn US-dollars will become off patent<sup>5)</sup>.

Assuming a conservative market share for biosimilars of 30 %, this might still be a 10 bn US-dollars market, providing companies sufficient incentive to develop biosimilars. It is not, however, the traditional generic players who invest in R&D and manufacturing plants for biosimilars. As recently as four to five years ago, it were traditionally strong generics players like Sandoz, Teva and Ratiopharm who invested in biosimilars, along with a handful of smaller, mostly Asian companies like Dragon, Biocon, Dr. Reddy's or Phage. Today, innovative, big pharmaceutical companies have taken over the field. Companies like Merck, Amgen, Boehringer Ingelheim, Pfizer, MSD and Sanofi dominate the landscape of biosimilars R&D (Fig. 4).

<sup>5)</sup> Cepton Research.

The explanation for this shift from generics players to innovative pharmaceutical companies is straight forward. Over the past few years, companies had to recognize that biosimilars are very different from generics. Regulatory requirements are similar to those of innovative products and R&D costs add up to 100 million US-dollars – 300 million US-dollars per target. The investment in production facilities far exceeds that of generics. Samsung recently invested 500 million US-dollars in a production plant for biosimilars on behalf of MSD and the cooperation between Lilly and

Figure 4

Company	1	2	3	4	5	6	7	8	9	10
AMGEN	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Boehringer Ingelheim	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pfizer	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
MERCK	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
MERCK	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Baxter	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
SANOFI										✓
Lilly										✓
S SANDOZ	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TEVA	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CELLTRION	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Mylan	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Biosimilar players today and their pipeline / portfolio (Source: Cepton Research).

Boehringer Ingelheim invested 1 bn US-dollars to prepare for the manufacturing of Lantus<sup>®</sup> biosimilars. Similar to the innovative business models, these huge investments won't pay off until many years from now.

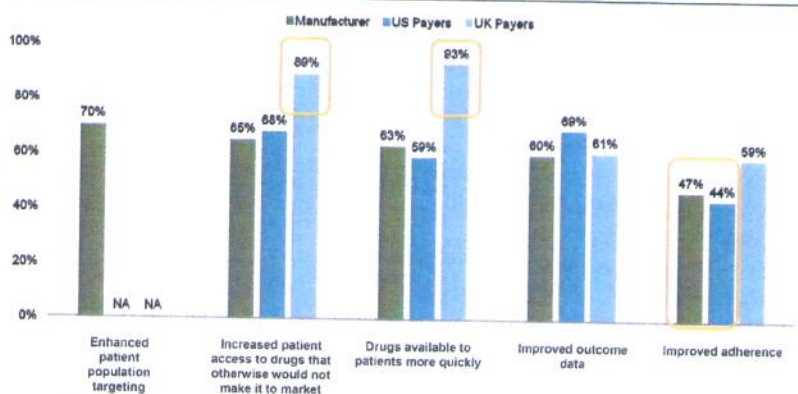
The requirements and investments described above are reason why – even with the existence of biosimilars – biological products are expected to remain in the higher priced segments. And this will secure the investments of innovative pharmaceutical companies in the field of biosimilars.

Sharing risk

Risk sharing and value-based pricing may seem rather new to today's pharmaceutical industry, but risk sharing agreements have been around longer than it might seem. Emerson, a pharmaceutical company that merged with Warner-Lambert Pharmaceutical in the 1950s, later integrated with Pfizer, advertised its Bromo Seltzer pain killer with the slogan "All headaches instantly cured or money refund".

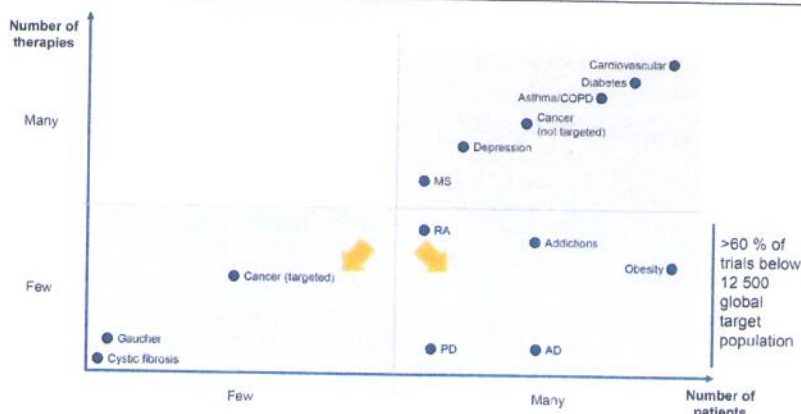
Today, pay-for-performance contracts can be found in almost all pharmaceutical markets around the world. Examples include Novartis'

**Figure 5**



*Reasons to introduce risk sharing from Pharma perspective (Source: Quintiles / Cepton Research).*

**Figure 6**



*Mapping of therapeutic areas based on the number of patients vs. number of therapies (Source: Cepton Research / EY/ KH).*

Lucentis<sup>®</sup> that does not ask for the payment of any required cycles after the 14<sup>th</sup> treatment in the UK, or Novartis' Aclasta<sup>®</sup> that offers refunds in Germany and Italy if the treatment fails. Some examples even set incentives to improve compliance, such as Merck's Januvia<sup>®</sup> which provides increasing discounts with patients reaching certain blood-sugar goals and further discounts if patients take the drugs as prescribed.

From a pharmaceutical company's perspective, risk-sharing agreements mainly target access and speed of market entry (Fig. 5). Especially for a second or third product on the market for a given indication, reaching outcome-based or pay-for-

performance agreements with payors is often the only chance to gain a share of patients at a decent price.

As with many new models, outcome-based remuneration schemes raise questions, yet to be answered. For example, imagine two patients, who both require the same therapy and dosage, which consequently involves the same therapy cost. One patient is highly compliant, takes good care of him-/herself and shows good outcomes. The other patient keeps forgetting his/her medicine and does not take care as required. There may even be a difference in the quality of care provided by different physicians. In a typical outcome-based payment scheme, this would

represent the efficacy of the specific therapy. Depending on the outcome-based contract, this scenario could result in no payment for the therapy even though the quality of the drug has been high. As soon as payments are linked to the individual success of the therapy per patient, differentiating patient behaviour from therapy efficacy becomes difficult.

### Re-designing R&D and teaming-up to win

The pharmaceutical industry has always been one of the most innovative industries, investing heavily in R&D. Between 2004 and 2011, investment in R&D had an annual compound growth rate of +6.6%. But decreasing R&D output and ever increasing R&D cycles finally led to a decrease in R&D investments and the R&D spending worldwide decreased between 2011 and 2013. Today, global R&D spending is stagnating.

As future patient population sizes are much smaller than they used to be, the focus of R&D has shifted. The majority of R&D activities take place in indications with less than 12 500 patients worldwide (Fig. 6). Part of this is market access tactics, aiming for market access authorization with a small patient population and targeting additional patient segments later on. But that is only part of the story. No doubt, we see that the focus of R&D activities has shifted to smaller patient populations.

Analysis of the top 20 most valuable R&D projects by projected sales in 2018 reveals even more particularities in the field of R&D (Fig. 7). First of all, R&D pipelines are rarely filled only with future blockbusters. Additionally the landscape of players has changed. Instead of naming all the Big Pharma companies, the list is filled with small biotech players. The therapeutic areas' focus is clearly on a few indications, highly dominated by the oncology field. Other than oncology, some Hepatitis C and some HIV

■ Figure 7

	Product	Company	Phase	Pharmacological Class	Indication	WW 2018 Sales (\$m)	Today's NPV (\$bn)
1	Sofosbuvir	Gilead Sciences	Filed	Hepatitis C nucleoside NS5B polymerase inhibitor	Hepatitis C	7,352	28,566
2	BMS-936558	BMS	Ph. III	Anti-programmed death-1 MAb	Oncology	1,869	9,912
3	GS-7977/GS-5885	Gilead Sciences	Ph. III	Hepatitis C nucleoside NS5A & NS5B polym.inhib.	Hepatitis C	2,217	6,845
4	IMC-1121B	Eli Lilly	Filed	Anti-VEGFR MAb	Oncology	970	4,232
5	Ibrutinib	Pharmacyclics	Ph. III	Bruton's tyrosine kinase (BTK) inhibitor	Oncology	1,401	4,040
6	Reolysin	Oncolytics Biotech	Ph. III	Oncolytic virus - Ras activated	Oncology	1,127	3,887
7	VX-809 + ivacaftor	Vertex Pharma	Ph. III	CF transmemb. conductance regulator corrector	Cystotic Fibrosis	1,427	3,538
8	RG3638	Roche	Ph. III	Anti-mesenchymal epithelial transition MAb	Oncology	656	3,478
9	Palbociclib	Pfizer	Ph. III	Cyclin-dependent kinase 4 & 6 inhibitor	Oncology	794	3,151
10	LY2062430	Eli Lilly	Ph. III	Anti-beta amyloid MAb	Alzheimer's Dis.	726	3,083
11	Odanacatib	Merck & Co	Ph. III	Cathepsin K inhibitor	Osteoporosis	921	2,504
12	Dolutegravir	GlaxoSmithKline	Filed	HIV integrase inhibitor	HIV	1,284	2,473
13	Opsumit	Actelion	Filed	Endothelin receptor antagonist	Pulm. Art. Hypert.	927	2,421
14	BAX 817	Baxter	Ph. III	Factor VIIa	Hemophilia A	470	2,416
15	LY2963016	Eli Lilly	Ph. III	Insulinalgargin biosimilar	Diabetes	522	2,362
16	REGN727/SAR236553	Sanofi	Ph. III	Anti-PCSK9 MAb	Cholesterol	621	2,100
17	Apremilast	Celgene	Filed	Phosphodiesterase IV (PDE4) inhibitor	Auto-Immune	605	2,018
18	Afrezza	MannKind	Ph. III	Insulin	Diabetes	286	1,985
19	Riociguat	Bayer	Filed	Guanylate cyclase activator	Pulm. Hypertens.	732	1,950
20	Anoro Ellipta	GlaxoSmithKline	Filed	LAMA & long-acting beta 2	COPD	882	1,941

**Most Valuable R&D Projects (Source: Cepton / EvaluatePharma).**

projects are listed. Diabetes, which used to be pharma's big flagship, is only represented by one single project – Eli Lilly's program for the Lantus® biosimilar, not even an innovation at all.

Changes in R&D activities affect licencing deals as well. In total, there is a declining number of licencing deals and a growing number of partnering deals. Big Pharma's tactic to fill gaps in its pipeline by in-licencing late stage, phase II R&D projects has not paid off. Late stage R&D projects have become too expensive. Big Pharma is now entering into partnerships at an earlier stage, trying to be in on the ground floor with innovative opportunities and sharing risk with partners.

By all indications, pharmaceutical companies today build global networks of long term partnerships with academia, start-ups, other Big Pharma players, diagnostic companies and many more join forces on R&D activities. There are countless examples of these diverse networks. In the area of melanoma, GlaxoSmithKline established a part-

nership with Pfizer, allowing it to collaborate on research of the combination of Palbociclib (Pfizer) with Trametinib (GSK). In a research project for antibacterial therapies GSK is leading a platform which combines 32 partners from 13 countries as part of the European Gram-Negative Antibacterial Engine. GlaxoSmithKline is collaborating with the University of Edinburgh on research projects for acute pancreatitis and liver diseases. With the foundation of the independent company, ViiV, GSK and Pfizer have transferred all knowledge and R&D assets in HIV and combined commercial forces. GSK also established its own venture capital fund, aiming to pioneer investment in bioelectronic medicines and technologies.

Today, most big pharmaceutical companies have established similar corporate venture capital funds. Novartis has 550 million US-dollars and almost 50 companies under investment. Roche spent the same amount of money for about 30 innovative start-up companies. Astra-Zeneca's venture fund is called

MedImmuneVentures and has approximately 400 million US-dollars under management. Lilly's fund, Lilly Ventures, has 200 million US-dollars and about 20 young companies under management – just to name a few. These funds clearly aim to support highly innovative start-ups and get an early hold on innovative therapeutic and diagnostic approaches. Most of the funds target a broad field of indications and approaches. Funds like Roche Venture Fund show a clear focus on oncology and companies that specialize in research on personalized medicine and antibody treatments are the exception.

### Digitalizing

While everybody is taking about digital healthcare and health 2.0, Big Pharma often uses their venture capital funds to gain access to innovative business models in this field.

MSD's fund, Global Health Innovation, is among the top funders of digital health start-ups, with investments of more than 250 million US-

dollars in 15 aspiring companies. These start-ups deal with cloud computing and services to integrate, transform, harmonize, manage and secure bid data on individual patient information in a data cloud. Considering the impact that the availability of large sets of real-life patient data would have on phase IV trials and the cost-benefit discussion, the potential of this approach becomes obvious. Other approaches are much closer to patient management, providing point-of-care mobile solutions that orchestrate people, data, and processes in real-time.

Roche Venture Fund takes patient management a step ahead, funding a company that provides implants for patients, serving as a monitoring sensor that will feed back medical data, such as blood glucose to caretakers and physicians. Other start-ups work on more controversial approaches, such as 23andMe, which provides information on genetic codes directly to the patient. This raises questions about what the patients will do with information on the likelihood to develop a serious disease many years from now if there is no cure in sight? Will this influence the possibility of patients obtaining health insurance? How do we prevent other parties, e.g.

future employers, from gaining access to this information?

#### Future outlook on our healthcare systems

There is a high level of innovation in healthcare today. Big Pharma continues to invest heavily in innovative therapies and diagnostic options. In recent years, Big Pharma has also identified new approaches to business models, outcome-based pricing schemes, R&D activities and partnering. Looking ahead 10–20 years from now, will the changes initiated today be the ones shaping the future?

It is likely that

- Personalized medicine becomes routine, and people are treated with regard to their genetic code rather than a disease, everybody having chip implants for identification, medical records and measuring of vital functions.
- In most cases, the likelihood to develop a disease is identified before birth or at early childhood and patients identified to be at risk for a disease will receive immediate prevention care.
- Close loop systems and device driven organs are established by

Big Pharma, medical device consolidation and innovation is driven by diagnostics, gene labs and IT partnerships.

- Apps guide patients and doctors to treat according to standards of care. Telemedicine provides patients access to highly specialized care without limitation and healthcare data stored as electronic patient files in a cloud, accessible by all providers.
- Providers underline selective contracting by certain payors and these payors have treatment guidelines and comprehensive payment schemes based on treatment outcomes.

Chip implants and routine DNA testing may seem many years off. On the other hand, part of this is already becoming reality. Strategies are changing today? They will need to change even more in the future.

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