



Catenion Strategies, GmbH

**David A Campbell,
Matthias Krings,
Markus Thunecke &
Christian Elze**

*Catenion Strategies,
Hausvogteiplatz 12,
10117, Berlin, Germany
Tel.: +49 30 20639960;
E-mail: Info@catenion.com;
www.catenion.com*

Catenion Strategies is a strategy consultancy company formed around a long-standing team of Anglo-German partners of various scientific and industrial backgrounds with a common passion for the dynamics of the life-science industry. Catenion provide strategy consulting services exclusively for the top management of pharmaceutical, biotechnology and diagnostics companies. Their focus lies in the areas of corporate development, research and development (R&D), therapeutic area and product strategy, as well as in the emerging field of personalized medicine. Catenion believe their grounding in R&D is unique, and they aspire to be the premier partner of choice for senior management in all core aspects of shaping pharmaceutical strategy.

The partners' backgrounds and experiences range from pharmaceutical research and development (R&D) in major CNS indications, to global strategy consulting and disease management strategies, and from translational medicine and clinical development in biotechnology and pharmaceutical companies to molecular evolution and human genome diversity research.

The team's history began prior to the sequencing of the human genome and when the full brunt of the enabling technologies wave caught the life science industries. Against this background of periods of industry hypes and consolidations, Catenion have helped a growing number of international clients to maneuver through their individual company history and evolve to become some of the most respected organizations in the sector.

In parallel, Catenion have developed unique intellectual capital addressing in breadth and depth the essential items on most life science Chief Executive Officers' agendas: corporate development, research and development strategy, and therapeutic area and product strategy (see **Box 1** for a more detailed list).

In addition, Catenion passionately believes in the potential of personalized medicine, was an early advocate of the concept and has worked on the topic within major R&D organizations and for major international client organizations, in addition to in internal studies.

Aspects of personalized medicine *Background*

It is widely accepted that prescription drugs do not demonstrate efficacy in 100% of patients. Indeed, depending on the therapeutic area, the

efficacy ranges from less than 25% for some anti-tumour agents to over 80% for some of the new generation pain killers. In one aspect, personalized medicine aims to ensure that only those who will respond in a desired way will receive a particular drug (**Box 2**).

Obviously, few people would object to the desirability of the benefits of personalized medicine: no (or fewer) prescriptions in vain and therefore no delay in the start of appropriate therapy, no side effects and therefore no secondary condition to be treated, improved timing and dosing for individual patients, and through all this, no futile spending on inappropriate therapies. However, there are some commonly cited major obstacles – and less frequently mentioned counter arguments – as to why personalized medicine has not yet become a reality of medical practice.

Patient profiling and selection for treatment implies that potential patient populations will be reduced and the addressable market will only be a fragment of the overall prevalence in any given indication. The preferred blockbuster business model is of course based on the one-drug-fits-all concept. For the large pharmaceutical corporations that have built immense marketing power over the past decades, this poses a threat to the principal business model, as multibillion dollar sales may not be achievable on subpopulations. In contrast, small and mid-sized companies experiencing difficulties in competing with such marketing power may gain additional differentiating factors by offering an efficacy or safety prediction test to accompany their drug. Furthermore, initial approval in a niche indication does not necessarily mean that a drug will be efficacious only in this

Keywords: corporate development, management consulting, personalized medicine, product strategy, research and development strategy, strategy, therapeutic area strategy

future
medicine

Box 1. Catenion product offerings.

Corporate strategy

- Any successful strategy is characterized by five hallmark qualities: consistency, connectivity, perseverance, flexibility and a sense of purpose.
- Catenion have supported global pharmaceutical, biotechnology and diagnostics companies in defining their strategic roadmap for the next decades.

R&D strategy

- Leading-edge R&D Portfolio Management and R&D Productivity Management systems that have provided a solid basis for R&D strategy design.
- Catenion's asset assessment tool has been built based on the evaluation of more than 400 targets/projects/products across all phases of pharmaceutical R&D.
- Recombinant innovation management argues that the pharmaceutical industry's R&D is not only in a productivity crisis, but also in a creativity crisis. Organizational, process-related, governmental and cultural elements have been developed over many years to address the creativity factor in large R&D organizations.

Therapeutic area and product strategy

- A sophisticated approach to assessing the competitiveness of projects and products in their markets: the competitiveness model has been frequently used by clients both for strategic positioning and forecasting of project potential.

population, but may instead mean that the drug gets to market earlier than traditionally expected. With extensive lifecycle management and the addition of marketing power it is possible to turn such niche drugs into blockbusters.

The high sales of some pharmaceutical drugs are, of course, considered an appropriate and necessary return on the high investments in R&D that each company has to make. Estimates of R&D costs for a new drug range from US\$0.5 billion to more than US\$1.5 billion and timelines for R&D range from 8–12 years. These figures are attrition adjusted which means the costs for all the R&D projects that failed prior to reaching the market are included in the costs of the one project that did not fail. In addition to this, novelty and innovation attract additional costs, and there is general agreement that in order to stay innovative, pharmaceutical R&D will continue to require high investment, and will have to accept the high risk, and that this justifies a high return.

While high cost and project failures are to be expected in pharmaceutical R&D, there is constant effort to reduce cycle time, costs and attrition rates. Some skeptics of biomarker-based personalized medicine argue that biomarker programs run in parallel with drug R&D will result in exactly the opposite: additional effort will cost time, money and will, at best, reduce the addressable patient population. The biomarker program may also unearth critical findings on safety or may fail altogether, putting the entire drug project itself in jeopardy. This view is not entirely

unfounded, but is borne out of the traditional blockbuster business mentality: if the use of biomarkers is only applied reluctantly in late development phases, when there is no other option but to accept fragmented response patterns identified in Phase II clinical trials, it may indeed be an inadequate, tedious salvage attempt, rather than a strategic concept. In many cases this will be an attempt that the project team, and not least the organization, was not prepared for in terms of budget and timing, nor infrastructure or expertise.

The objective to deliver personalized drugs in R&D requires a completely different frame of reference. Only if biomarker programs are routinely run from the early phases of discovery, disease subpopulations are targeted from the start, certain metabolic pathways are excluded from the selection of the lead compound and mechanistic biomarkers are identified and subsequently validated to safeguard the project from preclinic to Phase II, does the concept of biomarkers become a strategic element.

Of course, for personalized medicine to come to full fruition, more players than just the pharmaceutical companies have to become involved. Certainly, pharma, biotech, diagnostics, healthcare providers, insurers, payers and, last but not least, patients will be part of the new paradigm. While it is almost too speculative to try and predict when and how the concept of personalized medicine will penetrate the healthcare profession, there are already examples on the market today, which are a significant first step in the direction of personalized medicines.

Box 2. Personalized medicine.

Personalized medicine is only thought of as enabling the prescription of ‘the right drugs, to the right patients, at the right dose and at the right time’, based on the combination of targeted drugs with diagnostic tests that allow the matching of patients with the drug and that allow guiding and monitoring treatment. However, Catenion take a more holistic view. Personalized medicine should have its roots firmly in global R&D strategy, and the company views personalized medicine as having a significant impact at all stages of the R&D continuum.

The key points of impact on R&D are embedded in three strategies observed to date:

- The insurance strategy – based on a broad R&D strategy a number of high profile drugs have failed over recent years. Given this, most organizations now aim to collect and archive biological samples from pivotal clinical trials. Having these samples ‘in the bank’ potentially allows organizations to rescue drugs that may otherwise have failed. Clearly this represents a high-risk approach since identifying and validating novel biomarkers of efficacy or safety still remains challenging. However, the commercial return can be significant if the efforts can truly save a failing drug.
- The translational medicine strategy – this strategy aims to demonstrate proof of concept (PoC) as early as possible after preclinical development. In the context of personalized medicine, companies profile drug candidates thoroughly in terms of efficacy and safety in preclinical *in vivo* models, drawing heavily on suitable biomarkers. While all organizations use PoC as a milestone in the development process, what appears to be new is the use of targeted clinical populations early in the development process in so-called PoC studies to show early signals of efficacy before significant decisions on investment are made. It is arguable whether this is really a new approach or just a redefinition of early clinical development. However, there is no doubt that most major organizations have a strong emphasis on this approach. The personalized medicine concept clearly plays an important role here since biomarkers for patient identification and stratification, as well as for early readouts of clinical benefit, are pivotal to the PoC strategy.
- The disease biology strategy – again disease biology is not new and most organizations focus significant discovery effort on attempting to understand the underlying biology of the diseases they aim to treat. However, this strategy focuses on known or emerging subsets of the patient population from the start of discovery programs, and never aims at a single drug for all patients in the given indication. The application of the personalized medicine concept at this stage is high risk. Many organizations have tried and failed to utilize ‘omic’ technologies to identify the next generation of targets.

Trastuzumab (Herceptin[®], Roche [Basel, Switzerland]/Genentech [CA, USA]) is a monoclonal antibody therapeutic that targets the Her-2/neu receptor on breast cancer tumors. This receptor is overexpressed in approximately 30% of women diagnosed with breast cancer. Levels of overexpression are assessed with molecular diagnostics tests, and only patients with elevated levels of Her-2/neu are treated with the drug.

Another example is imatinib (Gleevec[®], Novartis [Basel, Switzerland]). Imatinib is a small molecule therapeutic against chronic myeloid leukemia (CML). The majority of patients with CML harbor a faulty fusion protein termed Bcr-Abl that is encoded by the Philadelphia (Ph) chromosome, and imatinib targets this protein. There are diagnostic tests that determine the presence of the Ph chromosome and test-positive patients are then eligible for treatment with this drug.

Biomarkers in the R&D process

There are various phases of the pharmaceutical R&D process where biomarkers are routinely employed today, even without any intent for developing a personalized medicine.

Catenion classify markers into four broad categories:

- Mechanistic markers are used for increasing the level of confidence of *in vivo* activity of compounds in early signal search studies. Prediction of pharmacodynamic response may result based on, for example, forearm blood flow, delayed neo-vascularisation and wound healing, phosphorylation of targets, or fluorodeoxyglucose-positron emission tomography (FDG-PET).
- Disease markers are used for the prediction of disease likelihood, early diagnosis, differential diagnosis, and prognosis, for example, Bcr-abl for CML or Her-2/neu for breast cancer, Ras-mutations, epidermal growth factor receptor (*EGFR*) mutations or gene amplification.
- Surrogate markers are predictive of outcomes during and after treatment and are used for the early proof of positive outcome following treatment in clinical trials and in clinical practice. Examples include low-density lipoprotein (LDL) levels for cardiovascular risk, the lesion load for multiple sclerosis, levels of soluble vascular endothelial growth factor (VEGF), response evaluation criteria in solid tumors (RECIST), dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), or FDG-PET.

- Efficacy and safety markers are used prior to treatment for the prediction of outcome for a patient, and stratification or better characterization of patients in clinical trials. Examples include HIV drug resistance mutations, or cytochrome P450 (CYP) AmpliChip® for drug metabolism, *EGFR* mutation, or Her2/neu for trastuzumab.

Areas of growth for the personalized medicine market

There is no doubt that the therapeutic area where personalized medicine is having the greatest influence today is oncology. But what is driving this change? Through Catenion's experience of working with a number of major players in the oncology field they see two key drivers. The first is the significant shift from the development of cytotoxic drugs to the new breed of targeted therapies. The second is a result of this shift and represents the disappointing results that many of these agents have had in the clinic.

In order to support this growth, Catenion have been supporting the sector in two main ways. Firstly, through establishing a benchmark as to the strategic positioning of various companies in the field, and secondly through helping senior management to identify appropriate personalized medicine strategies for their companies.

Activity & positioning of major pharmaceutical companies in the personalized medicine arena

In an industry survey Catenion examined the impact of personalized medicine on the R&D portfolio of various pharmaceutical companies in terms of:

- Indications that the company is active in R&D
- Suitability of personalized medicine in those indications

- The overall estimated impact of personalized medicine on a company's portfolio

In addition, the relevance of personalized medicine as part of a company's overall strategy was assessed with regard to key diagnostic capabilities that had been established internally or externally through partnering. Companies included in the survey were Abbott (IL, USA), Altana (Konstanz, Germany), AstraZeneca (London, UK), Bayer (Leverkusen, Germany), BristolMyersSquibb (NY, USA), Eli Lilly (IN, USA), Genentech, GlaxoSmithKline (London, UK), Johnson&Johnson (NJ, USA), Lundbeck (Copenhagen, Denmark), Merck & Co. (NJ, USA), Novartis, Pfizer (NY, USA), Roche, Sanofi-Aventis (Paris, France) and Wyeth (NJ, USA).

Through the results of this survey Catenion were able to identify three types of company (Figure 1):

- 'Wait and see companies' have no internal biomarker groups, limited investment in technology, and only inconsistent collection of samples in clinical trials
- 'Building the option companies' show an overall defensive approach – 'we do it if we have to' – characterized by some deal-making and building of internal biomarker groups. These often have large investments in technology, routinely collect samples in clinical trials, but have no active positioning at the company strategy level.
- Strategic shaper companies actively position themselves in the personalized medicine arena at the company strategy level by selection design trials, sometimes proactively changing clinical decision-making, by routine collection of samples in all clinical trials, by very active deal-making, as well as by building strategic competencies internally, even if not necessarily building full-blown diagnostics (Dx) capabilities.

Catenion's contribution to personalized medicine

Catenion have extensive experience in both the pharmaceutical and diagnostic aspects of personalized medicine, ranging from individual compound strategies and action plans to business model choices at the company level. Catenion's value proposition is based on the insight that a company's adequate response to personalized medicine should be dictated by its portfolio composition.

Highlights

- With its roots firmly in the life sciences sector, Catenion Strategies aspires to be the premier partner of choice for senior management in all core aspects of shaping pharmaceutical strategy.
- Catenion focuses on corporate development, research and development strategy, and therapeutic area and product strategy.
- Since its foundation, the company has had an extensive focus on enabling the adoption, shaping and growth of personalized medicine, and is a strong proponent of the concept.
- Catenion have supported companies in building personalized medicine product strategies around late-stage products, and has helped in the organizational development of R&D to meet the challenge of parallel drug and biomarker efforts.

Catenion's Personalized Medicine Opportunity Assessment includes a systematic comparison of risk and value of a compound's baseline strategy with those of biomarker-based strategy. In addition, the screening rationales, technical feasibility and choice of technologies and diagnostics platforms are included in the validation process. Ultimately, companies will

know whether or not personalized medicine is relevant for their portfolio, where they can create or potentially destroy value, and how they can best prepare for the chance of personalized medicine gaining significant momentum. In other words, they will have an individually tailored strategy for the adoption of personalized medicine.

Figure 1. Strategic intent in personalized medicine.

