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Theranostics

Next stop: personalised medicine



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Life Sciences

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Life Sciences
Pharmaceuticals

FOCUS ON AN EMERGING AREA

Next step: personalised medicine

Personalised medicine seemed just a step away with the publication of the human genome in 2001. However, the concept did not hold an attractive business model for pharma, as it undermined the blockbuster paradigm; hence it has so far failed to take off. With healthcare costs exploding, payers and regulators are increasingly emphasising the cost-benefit ratio of a new drug, which is compromised if not all patients receiving the drug benefit from it. Meanwhile, some pharma companies have discovered that using theranostics can be attractive, as it can improve the results of clinical trials and shorten development times. We forecast that 'theranostics' is here to stay, with the integrated pharma/diagnostic firm likely to benefit most. Diagnostics companies look set to gain from this development, as it would give them a more important role in patient work-up, and may spark a takeover frenzy from pharma firms not wanting to be left behind.

- **What is theranostics?** Theranostics refers to the idea of combining diagnostics with therapeutics, to identify patient sub-populations that would benefit from treatment with a particular drug.
- **Theranostics is not pure bad news for pharma.** The biggest drawback of theranostics for the pharmaceutical industry is that it is likely to restrict the markets for its drugs in terms of patient numbers. On the other hand, identifying a biomarker early on during drug development could help save costs, by enabling smaller and more targeted trials showing better drug efficacy.
- **Theranostics is good news for diagnostics firms** as it would render their companion diagnostics gatekeepers for certain drugs, and hence give them more secure positions within patient work-up. Given the key positions of such companion diagnostics, they may be able to command higher prices than the average diagnostic.
- **Leaders and laggards amongst European pharma.** Of the seven European pharma companies in our coverage universe, Roche is the clear leader in theranostics, with its personalised healthcare policy and in-house diagnostics capability enabling it to involve diagnostics in early-stage research products. At the bottom end of the scale is Bayer, with no drug with companion diagnostic on the market and <1% of pipeline projects with biomarker programmes.

Ratings and target prices

Company	Rating
Current price	Target price
AstraZeneca	Reduce
2745.0p	2700.0p
Bayer	Add
€46.2	€52.0
GlaxoSmithKline	Add
1206.0p	1350.0p
Merck KGaA	Add
€67.4	€75.0
Novartis	Add
CHF 50.2	CHF 58.0
Qiagen	Add
€14.3	€15.8
Roche	Add
CHF 167.0	CHF 185.0
Sanofi-Aventis	Neutral
€50.1	n/a
Stratec Biomedical Systems	Neutral
€19.5	n/a

All prices as at close 24 September 2009

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Executive summary

What is theranostics?

Theranostics refers to the idea of combining diagnostics with therapeutics, to identify patient sub-populations that would benefit from treatment with a particular drug. Pharma companies have so far been reluctant to implement this concept, as it reduces the addressable markets of their drugs. However, attitudes are starting to change as healthcare payers put more and more emphasis on the cost-benefit ratio of drugs to help them contain the spiralling cost of healthcare. We thus believe that, despite the reluctance of pharma, it is only a question of time before theranostics gains importance. However, we also believe that this may not be pure bad news for the pharmaceutical industry.

Benefits and drawbacks for payers

The objective for the payer is to contain the overall cost of healthcare. For the payer, the benefits of theranostics are obvious. Restricting use of expensive drugs to those patients who stand to benefit from those drugs is likely to reduce the overall healthcare bill, even though more money may have to be spent on diagnostics.

Benefits and drawbacks for pharmaceutical companies

Pharmaceutical companies want large target populations at the same time as high prices for their drugs. The biggest drawback for the pharmaceutical industry is that theranostics is likely to restrict the markets for its drugs in terms of patient numbers. On the other hand, identifying a biomarker early on during drug development could help save costs, by enabling smaller and more targeted trials showing better drug efficacy. This would improve the likelihood that new drugs clear regulatory hurdles at the first attempt.

Benefits and drawbacks for diagnostics companies

For diagnostics firms theranostics offers significant benefits as it would render their companion diagnostics gatekeepers for certain drugs, and hence give them more secure positions within patient work-up. Furthermore, given the key positions of such companion diagnostics, they may be able to command higher prices than the average diagnostic.

The integrated pharma-diagnostic company is likely to benefit most

We believe that integrated pharma/diagnostics businesses are going to pull ahead in the long run in terms of benefiting from theranostics. Having in-house diagnostics expertise is likely to make it easier to involve diagnostics from an early stage onwards, without worrying about IP and confidentiality issues. Thus, the integrated company should benefit to a greater extent from any cost savings that the discovery of a biomarker could offer throughout the drug development process. We may hence see further takeovers of MDx companies, but we believe that Qiagen is an unlikely target despite its excellent position within the MDx market. Similarly, we do not believe Stratec is an immediate takeover candidate despite offering its customers the full design and manufacture of analyser solutions and possibly playing a key role in the field of theranostics in future, since the trend has traditionally been to outsource development rather than the other direction.

Pharma leaders ...

Within our pharma coverage universe Roche is the leader in terms of theranostics. Not only does it already have several drugs on the market that come with a companion diagnostic (e.g. Herceptin, Tarceva); it also has a personalised healthcare policy in place since the beginning of 2009 that stipulates that every pipeline project should have an associated programme to identify biomarkers. Furthermore, it has the advantage of having an in-house diagnostics unit. Merck KGaA and Novartis are hot on Roche's heels. Merck has already gained experience of theranostics through Erbitux (cetuximab) and a high percentage of pipeline drugs with biomarker programmes, and Novartis has founded a molecular diagnostics unit to facilitate biomarker research in its oncology franchise.

... and laggards

At the bottom end of the scale is Bayer, with no drug with companion diagnostic on the market and <1% of pipeline projects with biomarker programmes. Bayer's focus on specialty pharma and small molecules rather than antibodies may mean that biomarkers are currently not crucial to it. GlaxoSmithKline and AstraZeneca both have theranostics, thanks to the experience they have gained with the targeted oncology therapies Tykerb (lapatinib) and Iressa (gefitinib), but they can by no means claim to compete currently with the likes of Roche. Nevertheless, neither company intends to be left behind; both have stepped up their efforts in personalised medicine in recent years. Similarly, Sanofi-Aventis is in the early stages of looking into the merits of theranostics. If regulators and payers really start pushing stratified medicine, these laggards may have to dedicate more resources to theranostics in the coming years in order to catch up with their peers.

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Theranostics – what’s the fuss?

Theranostics refers to the idea of combining diagnostics with therapeutics, to identify patient sub-populations that would benefit from treatment with a particular drug. Pharma companies have so far been reluctant to implement this concept, as it reduces the addressable markets of their drugs. However, attitudes are starting to change as healthcare payers put more and more emphasis on the cost-benefit ratio of drugs to help them contain the spiralling cost of healthcare. We thus believe that, despite the reluctance of pharma, it is only a question of time before theranostics gains importance. However, we also believe that this may not be pure bad news for the pharmaceutical industry.

What is theranostics, and how could it be used?

Theranostics refers to the rapidly evolving idea of combining diagnostics with therapeutics, to identify patient sub-populations that would benefit from treatment with a drug.

There are basically four applications in which theranostics can be used:

- Predisposition profiling: evaluating inherited predisposition to various diseases (only useful if prophylactic exists).
- Screening/diagnosis: enabling detection of disease before symptoms occur (e.g. HPV test for cervical cancer).
- Patient stratification: supporting rational pharmacotherapy under efficacy and safety considerations (providing the right drug for the right patient, e.g. Herceptin only for HER2-positive patients).
- Therapeutic monitoring: constantly monitoring a patient’s response to treatment or the therapeutic efficacy, and accordingly assisting physicians in recommending a course of action (which could result in improved patient compliance due to a positive feedback loop).

We shall concentrate here on theranostics for the purpose of patient stratification, in particular on those applications that use molecular markers as biomarkers to identify patient groups that might benefit from a particular drug.

The economics of theranostics

In terms of the economics of theranostics, there are three major stakeholders: the healthcare systems or payers that foot the bills, the pharmaceutical industry, and the diagnostic industry. Obviously, these players each have different interests:

- The payer wants to contain costs and get value for money.
- The pharmaceutical companies want ‘blockbuster’ drugs, which usually tend to be associated with use in large patient populations, and high prices to recoup the development costs for its drugs.

- Diagnostics companies want diagnostics to play a more important role within patient work-up, which not only would enlarge their markets but could also allow them to charge higher prices for their products.

Stakeholders and their objectives

Stakeholder	Objective	How to achieve objective	Effect of theranostics
Payer	Value for money	Save costs while ensuring optimum outcome	↑
Pharma	Recoup drug development costs, ensure profitability	Large target patient pool	↓
		High prices for its drugs	↑
Diagnostics	A larger slice of the healthcare market	More prominent role for diagnostics in patient work-up and follow-up	↑
		Higher prices for diagnostics	↑

Source Companies, WestLB Research

We will look at the benefits and drawbacks of theranostics for each of these three different stakeholders in the following three sections.

The regulator and healthcare payer

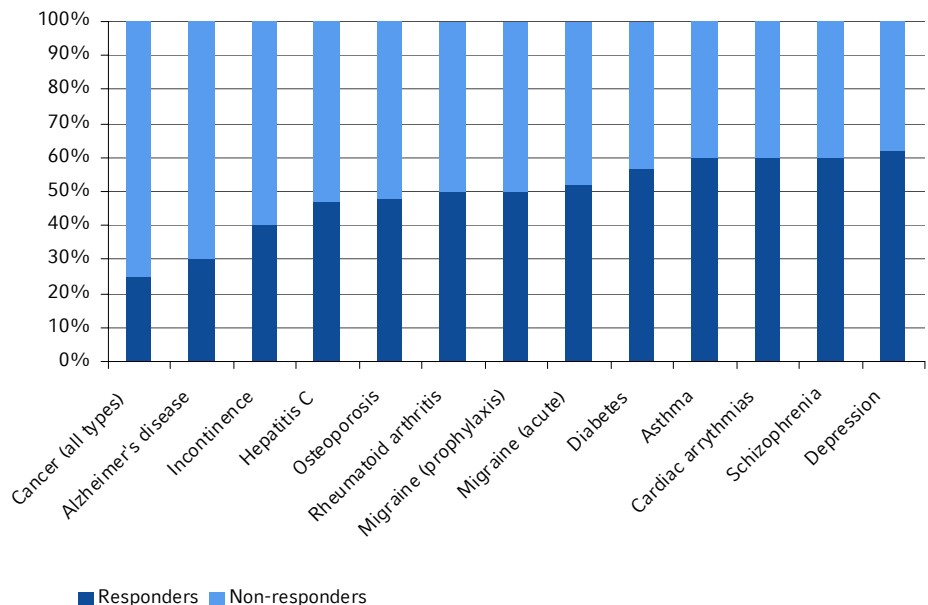
Most healthcare system are trying to contain costs

Most healthcare systems in the developed world are struggling with the rising costs of these systems, e.g. in the USA, growth of healthcare spending per capita (average 8.8%) has been outstripping GDP growth (average 6.1%) for years. With increasing pressure to contain costs within healthcare systems, payers have an interest in getting more value for the money they spend, and theranostics could do just that through improving a drug’s cost-benefit ratio.

Theranostics has the potential to save costs and reduce the incidence of ADRs

Many drugs only work in a small percentage of patients in any given indication. Identifying those patients who are most likely to benefit from such a drug, and excluding those that may not benefit from treatment with it, will not only save costs; it will also spare patients who fail to benefit from the drug from experiencing the often hefty adverse drug reactions (ADRs) that those drugs may elicit.

Rate of efficacy with standard drug treatment



Source Spear et al.: 'Clinical Application of Pharmacogenetics', Trends in Molecular Medicine, 2001

Examples of drugs with companion diagnostics for patient stratification

Company	Drug	Indication	Biomarker	% of patients benefiting from drug	Cost of drug	ADRs
Roche (Genentech)	Herceptin	HER2+ breast cancer	HER2	c. 20-30%	c. \$3,000/month	Cardiac dysfunction (2-7% of cases)
Imclone (Eli Lilly), BMS, Merck KGaA/Amgen	Erbix/Vectibix	mCRC, SCCHN	EGFR, KRAS	c. 60% in mCRC	Erbix: c. €3,600/month Vectibix: c. €3,000/month	Acne-like rash, cardiopulmonary arrest, pulmonary toxicity

Source Companies, WestLB Research estimates

Biomarkers that are used to identify patients at increased risk of ADRs

For some drugs biomarkers are used to identify patients at risk of serious and sometimes fatal ADRs, so that they can either be excluded from treatment or receive a lower dose that is deemed safe for them. Examples of this would be the HIV drug abacavir, where patients harbouring the HLA-B*5701 gene variant are at risk of developing hypersensitivity reactions that can be fatal; and the cancer drug irinotecan, where patients homozygous for a specific UGT1A1 gene variant have an increased risk of developing neutropenia (a type of immunosuppression).

Some examples of drugs where a biomarker is used to identify patients at high risk of ADRs

Drug company	Drug	Indication	Biomarker	% of patients at risk of severe side-effects	Cost of drug	ADRs
GSK	Abacavir	HIV	HLA-B*5701	c. 10%	\$3,540/year	Severe, sometimes fatal hypersensitivity reaction
Yakult Honsha/Pfizer	Irinotecan (Camptosar)	Colon cancer	UGT1A1	c. 9%	\$10,000/ 8-week regimen	Neutropenia, severe diarrhoea

Source Companies, WestLB Research estimates

ADRs are a huge burden, not only on the patient but also on the healthcare system

Apart from being a burden on the patient ADRs can cause substantial costs to the healthcare system. Various studies estimate that 4-7% of all hospital admissions are due to ADRs. Estimates of the cost of ADRs to healthcare systems vary widely, depending on which factors are included. For the US healthcare system, estimates range from \$77bn to \$340bn, which is a substantial burden even at the low end.

Payers are waking up to the benefits that theranostics could offer

Thus, despite the obvious need to pay for the diagnostics, theranostics offers huge benefits to healthcare systems in terms of both cost savings and patient outcome. Indeed, healthcare policymakers seem to be waking up to this fact. For example, the Obama administration's Recovery Act includes \$1.1bn for research to give doctors tools to make the best treatment decisions for their patients, by providing objective information on the relative benefits of treatments.

Payers need to push through reforms and legislation to support theranostics

If payers want to take advantage of the significant benefits theranostics could offer them, we believe they have a major role to play, as they have both the incentive and the clout to push through reforms and legislation in favour of theranostics. Benefits to pharmaceutical companies are not so obvious, and hence they have been reluctant to co-develop diagnostics with their drugs to identify patients who would most benefit from a particular drug.

The implications of theranostics for the pharmaceutical industry

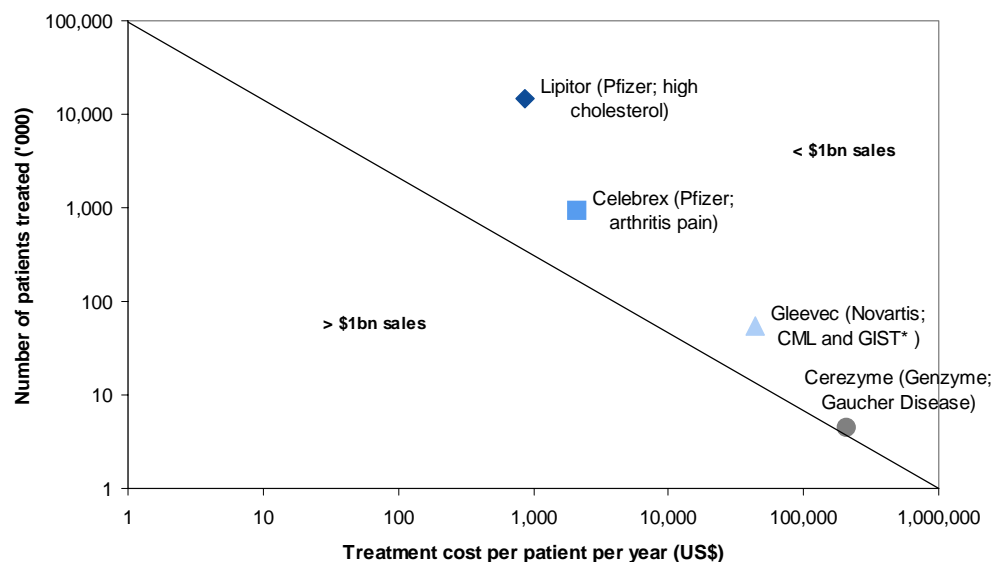
Theranostics does not necessarily mean the end to blockbusters

Until recently, the pharmaceutical industry has shied away from the idea of theranostics, as it ultimately leads to personalised, or rather stratified, medicine. Stratified medicine would undermine big pharma's blockbuster model, as it would shrink the broad patient pools previously targeted. On the other hand, it means that those patients who would benefit from a drug are more likely to receive it, and healthcare providers may be more willing to pay the premium prices charged for such drugs.

How to achieve blockbuster status

As can be seen in the chart below, blockbuster status can be, and is, achieved by two different approaches.

Different types of high-revenue medicines



*CML: chronic myeloid leukaemia; GIST: gastrointestinal stromal tumour
Source MIT Center for Biomedical Innovation, WestLB Research estimates

Traditional blockbusters target a high number of patients but are relatively 'cheap'

Traditional blockbusters such as Pfizer's Lipitor and Celebrex target as broad an indication as possible, with sometimes millions of patients potentially eligible for treatment. However, most blockbusters are effective in only 40-60% of patients. Furthermore, several similar and somewhat undifferentiated products are often competing for patients. Hence, there is an upper limit to how much companies can charge for these drugs. Prices are also kept at bay by the sheer size of the markets these drugs target, as no healthcare system would be able to afford the same high prices for them as are often paid for targeted or orphan drugs. Hence, prices for traditional blockbusters have an upper limit, e.g. Lipitor costs \$871 per patient per year while Celebrex costs \$2,100.

Niche busters target a limited number of patients but prices can be very high

On the other hand, 'niche busters' such as targeted drugs (e.g. Gleevec) and orphan drugs (e.g. Cerezyme) that achieve annual sales of \$1bn and more are often highly differentiated, and sometimes even the only drug targeting a specific disease. Despite targeting only very limited patient pools (often only a few thousand patients), these drugs achieve high annual sales through the high prices companies can charge for them (\$44,000 per patient per year for Gleevec and \$207,000 for Cerezyme), due to their highly

differentiated status. Thus, developing drugs for smaller indications can prove to be very attractive indeed.

Theranostics could lead to lower drug development costs

One of the key challenges for the pharmaceutical industry today is derived from the escalating costs and decreasing productivity of research and development. This development is largely driven by an ever increasing need to demonstrate clinical efficacy and cost-effectiveness of new medicines, and tougher demands on a drug's safety profile. As these issues need to be addressed before the product can be launched, this increases product development times, and hence decreases the scope of opportunity yielded by the patent life of the drug.

With the emergence of new treatment modalities such as the targeted therapies that have resulted from a better understanding of the molecular mechanisms underlying certain diseases, the R&D costs and development times are likely to continue to rise. This is mainly because the efficacy of these targeted therapies varies significantly based on an individual patient's pathophysiology and genetic make-up. The selective use of biomarkers could address these challenges.

Biomarkers could assist in selecting better responders for clinical trials, thus reducing the size of the trial sample required to show statistically significant efficacy of the drug. A biomarker could also serve as surrogate for a longer-term endpoint such as overall survival, thereby reducing the length of time a trial needs to be run for.

In some cases, the use of biomarkers could also spur faster regulatory review cycles. Two parameters that regulators take into account when considering a drug's approval is the drug's risk-benefit ratio and superiority to existing treatments. Clearly, enriching a trial for responders will ensure superior efficacy data over a trial that is not enriched for responders; this would have a positive impact on both these parameters. Gleevec, for example, for which a test exists that can identify responders, was approved by the FDA within three months, with a total elapsed time from first human dose to FDA approval of under four years. This compares favourably with the average time for a drug from entering the clinical phase to approval of 8.5 years.

There is, of course, the possibility that biomarkers will increase R&D costs by making it necessary to find a corresponding biomarker for a drug. Furthermore, trial length could increase due to the biomarker-driven higher exclusion rates.

Theranostics could have a positive impact on reimbursement decisions and pricing

When it comes to pricing of a drug, one question that needs to be addressed is: how much will healthcare payers be willing to pay for this? Of course, the answer to this question varies from country to country, but payers are increasingly emphasising cost-benefit ratios of a particular drug, i.e. how much the drug costs and what it delivers for that price in terms of patient outcome (e.g. extended survival, better quality of life, disability improvement) when it comes to deciding reimbursement rates.

An improved cost-benefit ratio can swing the payer's decision on whether to reimburse a drug, and theranostics could significantly influence this ratio, as the benefits in a patient pool enriched for responders are much larger than in the entire patient pool. For

Key challenge is to rein in costs and increase productivity of R&D

Targeted therapies are likely to increase R&D costs if current trends continue

Use of biomarkers could address this problem ...

... and result in shorter regulatory review cycles ...

... but they could also increase R&D costs and trial times

Reimbursement decisions often take cost-benefit ratios into account

Theranostics can improve the cost-benefit ratio of a drug ...

example, use of Merck KGaA's Erbitux in metastatic colorectal cancer (mCRC) was initially not reimbursable on the UK's National Health Service as it did not meet the stringent cost-benefit criteria of the National Institute of Clinical Excellence (NICE). Only once patients that would benefit from treatment with Erbitux could be identified through the KRAS biomarker, did NICE back Erbitux in mCRC (albeit after Merck granted it a discount on the price of the medicine).

... and allow for higher pricing

Higher measurable benefits in a stratified patient pool could also allow a company higher pricing of its drug. A higher price would obviously have a negative impact on the cost-benefit ratio, but if the benefit is sufficiently improved, a higher price may well be justifiable. Thus, identifying biomarkers for stratification early on in the drug development process, and already using them for patient stratification for the Phase III trial, would not only have the potential to cut costs in the development process, but would also enable the company to better recoup development costs later on through higher prices for the drug.

Theranostics could result in faster market penetration by a drug ...

Theranostics offers further advantages in terms of SG&A costs and IP position

If a patient is diagnosed with a disease and found to have the biomarker that indicates response to drug X, he/she is likely to receive drug X and not any other competitor drug for which outcome in this particular patient is unclear. This should result in reduced time to peak sales, and reduced sales and marketing costs, for a drug.

... and extend patent protection

Furthermore, adding a diagnostic test to a drug could extend patent protection beyond the expiry of the medicine patent.

Some thoughts on the costs and paybacks of theranostics for pharma players

The table below outlines several scenarios for the costs of drug development and the potential paybacks for a drug. For these scenarios we assume that the length of the patent life (20 years) is not going to change over the years.

The payback ratio for a recently approved drug is around 4

The first column describes the situation for recently approved drugs. A reasonably successful drug with \$500m annual sales, resulting from a development programme that cost \$1bn and took 10 years, has an effective patent life of 10 years. Assuming 80% gross margin, this drug would yield a payback ratio (defined as the ratio of the lifetime gross profit and the development costs) of 4.

If current trends persist, the payback ratio for a drug in the future could fall to 3

The 'Current trend' column describes what happens if all these parameters continue to develop as they have over past years, i.e. higher drug development costs, longer development times and sinking gross margins. In this scenario a drug would have to achieve annual sales of \$2bn even to yield a payback ratio of 3.

If theranostics delivers on all fronts, the payback ratio could hit 9.6

The 'Bright future' column assumes that all parties fully support theranostics. In this scenario, development time would be reduced to 5 years. With a patent life of 20 years, this would result in the drug's sales life increasing to 15 years. Development costs would fall from \$1bn to \$250m, mainly due to reduced failure rates but also owing to smaller trial sizes. In this scenario, even with average annual sales of only \$200m, and assuming a gross margin similar to that of today's drugs, the payback ratio would be a staggering 9.6, compared with 4 today.

More conservative assumptions yield a payback ratio of 4.3

A somewhat less optimistic set of assumptions brings us to the 'Sustained future' column, where we assume that drug development time, and hence sales life, will remain the same as it is today. Assuming that the use of biomarkers will bring down development costs, average annual sales of just \$330m at a gross margin of 65% would still yield a payback ratio of 4.3, and would thus be slightly superior to today's payback ratio.

Potential drug development futures

Parameter	Today	Current trend	Bright future	Sustained future
Patent life (years)	20	20	20	20
Development time (years)	10	14	5	10
Development cost (\$bn)	1	2	0.25	0.5
Sales life (years)	10	6	15	10
Average annual sales (\$bn)	0.5	2	0.2	0.33
Gross margin (%)	80	50	80	65
Lifetime gross profit (\$bn)	4	6	2.4	2.15
Payback ratio (x)*	4	3	9.6	4.3

*Lifetime gross profit/development costs **Source** MIT Center for Biomedical Innovation, WestLB Research estimates

We conclude that despite reducing the addressable market of a future drug, theranostics offers attractive opportunities for pharmaceutical companies.

Theranostics viewed from an MDx perspective

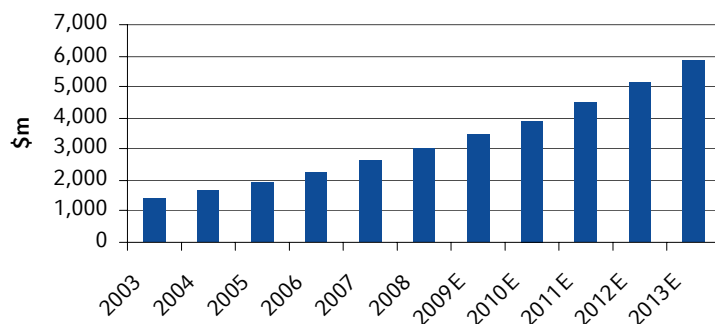
Theranostics is a bit of a double-edged sword for the pharmaceutical industry, but we believe the diagnostics industry can only gain from it. Not only could companion diagnostics command premium prices; we might also see pharmaceutical companies scrambling to snatch up previously shunned diagnostics assets. They may come to realise that having an integrated diagnostics business offers them advantages in terms of confidentiality, and enables them to get diagnostics involved in the drug development process at a much earlier stage – which could eventually result in cost savings.

The MDx market

The molecular diagnostics (MDx) market is a subsection of the in vitro diagnostics market. As the majority of emerging biomarkers are likely to be of a molecular nature, the MDx market is likely to benefit disproportionately from the increasing importance of theranostics.

In 2003 the global MDx market was estimated by Datamonitor to be about \$1.4bn. By the end of 2008 it had reached \$3.0bn (CAGR 2003-08: 16.3%) and Datamonitor expects it to continue to grow and reach \$5.8bn in 2013 (CAGR 2008-13E: 14%).

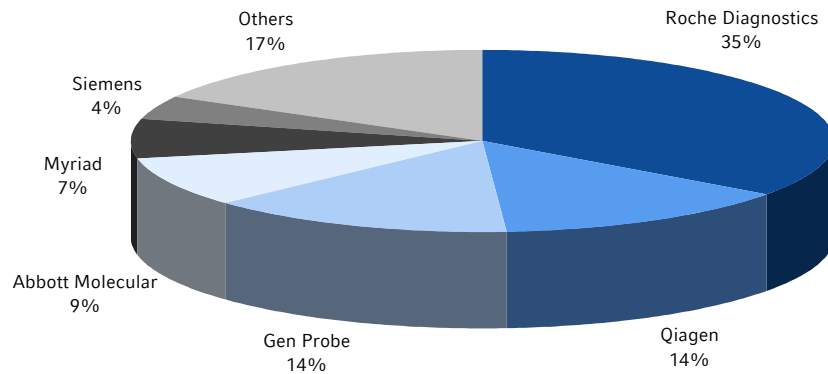
The molecular diagnostics market



Source Datamonitor, WestLB Research estimates

There are six major players in the MDx market, with a combined market share of 83%: Roche Diagnostics, Qiagen, Gen Probe, Abbott Molecular, Myriad and Siemens. The first three of these hold 63% of the market. With the recent acquisition of companion diagnostics company DxS, Qiagen is set to expand its market share further.

MDx market share by company, 2008

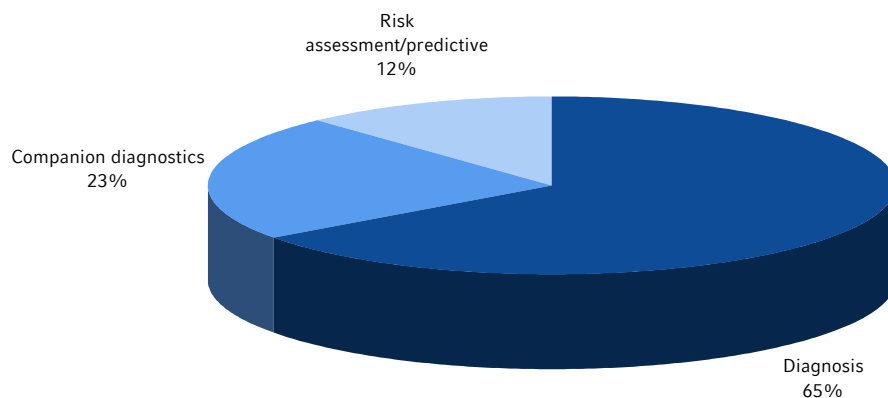


Source Companies, WestLB Research

Companion diagnostic tests made up only 23% of all available MDx tests in 2008. The majority of MDx tests (65%) on offer were for the diagnosis of a disease, rather than choosing the appropriate drug. This split reflects the fact that drug development firms have so far generally tried to avoid companion diagnostics for one of their drugs whenever possible.

However, with increasing emphasis on a new drug’s risk- and cost-benefit ratios from the regulatory and healthcare payer side, the number of MDx companion tests is likely to increase in both absolute and relative terms.

MDx tests by function



Source Datamonitor, WestLB Research estimates

Theranostics offers significant benefits to diagnostics firms

Theranostic tests could command premium prices

Diagnostics companies have long been perceived as less high-value players than pharmaceutical companies. Thus, diagnostics players could benefit immensely from theranostics, as the close connection to delivering cost-effective therapy should allow premium pricing of the high-value theranostic test.

Diagnostics may become an integral part of therapeutics development

Furthermore, such a test could help the pharma player to contain the cost of drug development, by enabling it to tailor its clinical programme to those patients who would benefit from treatment. As a result, pharma companies are likely to incorporate such tests in their clinical development programme, and may well be willing to pay premium prices for such tests at this early stage.

So far pharma has shied away from co-developing companion diagnostics

So far diagnostics firms have struggled to convince pharma companies to collaborate with them on developing companion diagnostics for their drug candidates, as pharma companies worry about unnecessarily limiting their drugs' potential markets. In fact, to date there is no drug on the market where a companion diagnostic has been co-developed with a drug from the start. Typically, only if clinical trials do not show the desired effect and approval is unlikely to be gained in a broader indication have pharma companies been willing to search retrospectively for biomarkers that could identify patients where their drug candidate makes a statistically significant difference.

The tide is turning ...

However, we believe the tide may be turning, as payers are trying to contain the spiralling cost of healthcare, regulators are putting more emphasis on the risk-benefit ratio of a drug, and pressure to implement theranostics increases.

... and pharma is getting increasingly interested in diagnostics

In fact, pharma companies have started to wake up to this, as can be seen by a number of acquisitions and collaborations that have sprung up over recent years. Furthermore, it looks to us as though pharma is starting to appreciate value in diagnostics, as evidenced by Roche's acquisition in 2007 for \$3.4bn of the diagnostics company Ventana, which had annual sales of \$240m.

Some firms go for an integrated theranostics approach ...

There are generally two different approaches by pharma firms that are looking to jump onto the theranostics train. Some companies try to combine diagnostics and therapeutics under one roof. Examples of this would be Roche and (to a lesser extent) Abbott, J&J and Novartis (the latter formed its own MDx unit only in February).

Top 10 pharma companies and their in-house MDx capabilities

Company name	In-house molecular diagnostics capabilities	Description
Pfizer (inc. Wyeth)	x	n/a
Johnson & Johnson	✓	Veridex: Oncology (breast lymph nodes assay and FISH probes) Virco: HIV-1 drug resistance testing
GlaxoSmithKline	x	n/a
Bayer	x	n/a
Hoffmann-La-Roche	✓	The largest global MDx player
Sanofi-Aventis	x	n/a
Novartis	✓	Unit founded in February 2009; initially focused on oncology
AstraZeneca	x	n/a
Abbott Laboratories	✓	Abbott Molecular: Genetics, infectious disease and oncology
Merck & Co	✓ ¹	Abmaxis: Antibody engineering platform for the discovery and development of mAb products for therapeutic or diagnostic use; most likely primarily used for therapeutics

¹ Capability is there but most likely not used for diagnostics

Source Companies, WestLB Research

... while others prefer to collaborate with existing diagnostics players

Others choose to collaborate with diagnostics firms rather than build up their own diagnostics units. Examples here include Novartis with Gen-Probe, Pfizer with Monogram and Abbott, and GSK with Abbott.

Integrated pharma/diagnostics businesses are likely to benefit most

We believe that in the long run integrated pharma/diagnostics businesses are going to pull ahead in terms of benefiting from theranostics. Having in-house diagnostics expertise is likely to save time as, once a biomarker policy has been established, no contracts need to be negotiated and signed, and no confidentiality issues arise. This should enable the integrated company to get diagnostics involved at an earlier stage in the drug development process. Thus it should benefit most from any cost savings that the discovery of a biomarker could offer throughout the drug development process.

Further pharma-diagnostics takeovers likely

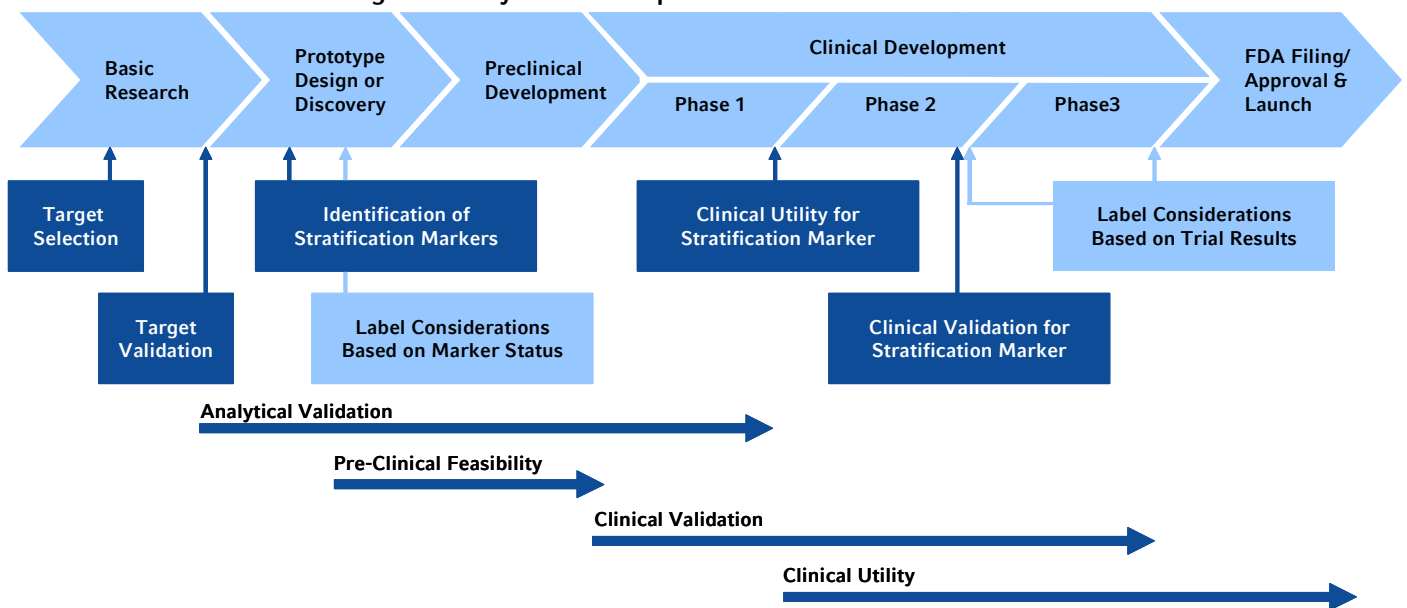
We may yet see further takeovers of diagnostics firms at hefty premiums as big pharma wakes up to the reality of theranostics.

How to integrate biomarker research into drug R&D

As previously said, in order to benefit from stratification markers throughout the drug development process and price the drug based on the patient population it is likely to be approved for, biomarker research should ideally be started at a very early stage of the drug development cycle and be an integral process of drug development rather than separated from it.

The chart below outlines how this could be achieved, with the stages of drug development shown in the upper part of the chart and the biomarker identification process below. Long before the drug enters clinical trials, possible stratification markers have been identified that not only contribute to shaping the drug's subsequent clinical development stage but also feed into the label (and hence pricing) considerations at various stages throughout the drug development cycle.

Biomarkers in relation to drug discovery and development



Source Adapted from Felix Frueh, FDA, 18th Annual DIA Euro Meeting

The integrated therapeutic/diagnostic company could obviously involve its diagnostic department from an early stage. However, where no internal diagnostics arm is available, the basic research to identify potential markers could probably be done in the pharma company's research labs, although involving a diagnostics company with its expertise in identifying biomarkers would probably be advantageous. However, when it comes to scaling up and standardising testing, i.e. in the run up to the clinical phase, a diagnostics company would definitely have to be brought in to design reliable tests.

Compared to a standard diagnostic kit, which often only takes 1-2 years to develop, such a companion diagnostic would have a much longer development time. To make such a prospect attractive for diagnostics companies, pharma is likely to have to pay for at least some of the development cost for the diagnostics as well as buy the tests used during clinical development from the diagnostic company.

Once the drug reaches the market, competitor diagnostics are likely to be developed. These may take away some of the original test's market share but as none of them is likely to be supported by the same amount of data as the original test, the original test is at a clear advantage.

The regulatory pathway for companion diagnostics

Europe only requires diagnostics to be CE marked

In terms of regulatory approval, diagnostics are classified as Medical Devices, and regulatory requirements vary hugely between the US and Europe. In Europe, they only need a CE mark. CE marking can essentially be done by the manufacturer and is nothing more than a label confirming that the item meets all the essential health and safety requirements of the relevant European Directives that provide for the CE mark. Generally, no lengthy clinical trials are required to confirm efficacy of the diagnostic device.

US regulators differentiate between 3 classes of Medical Devices

In the US on the other hand, Medical Devices are regulated by the FDA and depending on the class they fall into require a more or less stringent approval process.

FDA medical device classification

	Description	Examples	FDA label required	Data required for regulatory approval
Class I devices	Low-risk device, often simple in design	Tongue depressors, bedpans, elastic bandages, examination gloves, hand-held surgical instruments	510k unless exempt (majority are exempt)	Generally no clinical trials required
Class II devices	Medium-risk device, typically non-invasive; needs to show substantial equivalence to already approved devices	X-ray machines, powered wheel-chairs, infusion pumps, surgical drapes, surgical needles and suture material	510k unless exempt (only few are exempt)	Limited clinical trial data may be required to show that device is substantially equivalent to currently existing devices in terms of efficacy and safety
Class III devices	Only insufficient information exists for such devices to determine the device's safety and efficacy; often high risk medical device which poses a potentially unreasonable risk of illness or injury	Replacement heart valves, silicone gel-filled breast implants, implanted cerebral stimulators, implantable pacemaker pulse generators and endosseous (intra-bone) implants	Premarket Approval (PMA)	Clinical trial data is always required to ensure the device is safe and effective

Source FDA, WestLB Research

Most MDx tests fall into the Class II or III category, depending on the novelty of the test, and hence will require more or less time consuming and costly clinical trials before approval.

Current theranostics

There are already quite a number of drugs on the market that come with specific companion diagnostics. For an overview of current theranostics, see table Current Theranostics in the Appendix.

Case studies

A success story – Herceptin and the HER2 gene

Herceptin delays breast cancer progression in HER2 positive patients

Herceptin was developed by Genentech (now Roche) for the treatment of those 30% of metastatic breast cancer patients overexpressing the human epidermal growth factor receptor 2 (HER2). The protein is known to contribute to tumour development through stimulating cell growth and division. Herceptin could be shown to significantly delay disease progression in the targeted patient population, and was the first humanised monoclonal antibody approved by the FDA in 1998.

Approval was supported by a HER2 test to identify responders to Herceptin

Key to the approval was a diagnostic test from Danish diagnostics company DAKO that could identify patients that were overexpressing HER2 and would hence benefit from treatment with Herceptin. Herceptin would have stood little chance of getting approved without the test, as the drug's benefit in all breast cancer patients was not significant. DAKO's HercepTest was approved by the FDA on the same day as Herceptin.

Sales of \$4.7bn in 2008

The theranostics strategy certainly has paid off for Herceptin, with market penetration of around 95% in most Western markets and sales of \$4.7bn in 2008.

Herceptin sales

Sales (\$m)	2001	2002	2003	2004	2005	2006	2007	2008	01-08 CAGR %
Herceptin	672	840	982	1,197	1,790	3,276	4,048	4,701	32.0
growth yoy (%)	<i>n/a</i>	25.0	16.9	21.9	49.5	83.0	23.6	16.1	

Source Company, WestLB Research

Targeted Tykerb

GlaxoSmithKline had a very similar experience with its tyrosine kinase inhibitor Tykerb, the drug having shown to benefit the 25-30% of breast cancer patients who overexpress HER2. Tykerb differs from Herceptin due to its small molecular nature and its targeting of the HER2 receptor tyrosine kinase rather than the receptor itself.

The verdict is still out there: Erbitux, Vectibix, EGFR and KRAS

An example where the first biomarker didn't work

Erbitux (Imclone/BMS, Merck KGaA), a monoclonal antibody (mAb) targeted at the epidermal growth factor receptor (EGFR) that plays an important part in tumorigenesis, was initially approved in the USA and Europe for second and further lines of treatment of patients with EGFR expressing metastatic colorectal carcinoma (mCRC). On the same day in December 2004 that the FDA approved Erbitux, it also approved the DakoCytomation EGFR pharmDX kit for EGFR testing. However, it subsequently became clear that EGFR expression was not a good predictor of patient response due to the limitations of the test method used. Since then the marker and the test have lost significance, and both the FDA

and the EU's European Medicines Agency (EMA) have abstained from using the marker in further approvals of the drug in head and neck cancer.

As the importance of EGFR as a predictive biomarker for Erbitux waned, another biomarker emerged from analysis of the registration trial of Vectibix, another mAb targeted at EGFR that was then under development by Amgen.

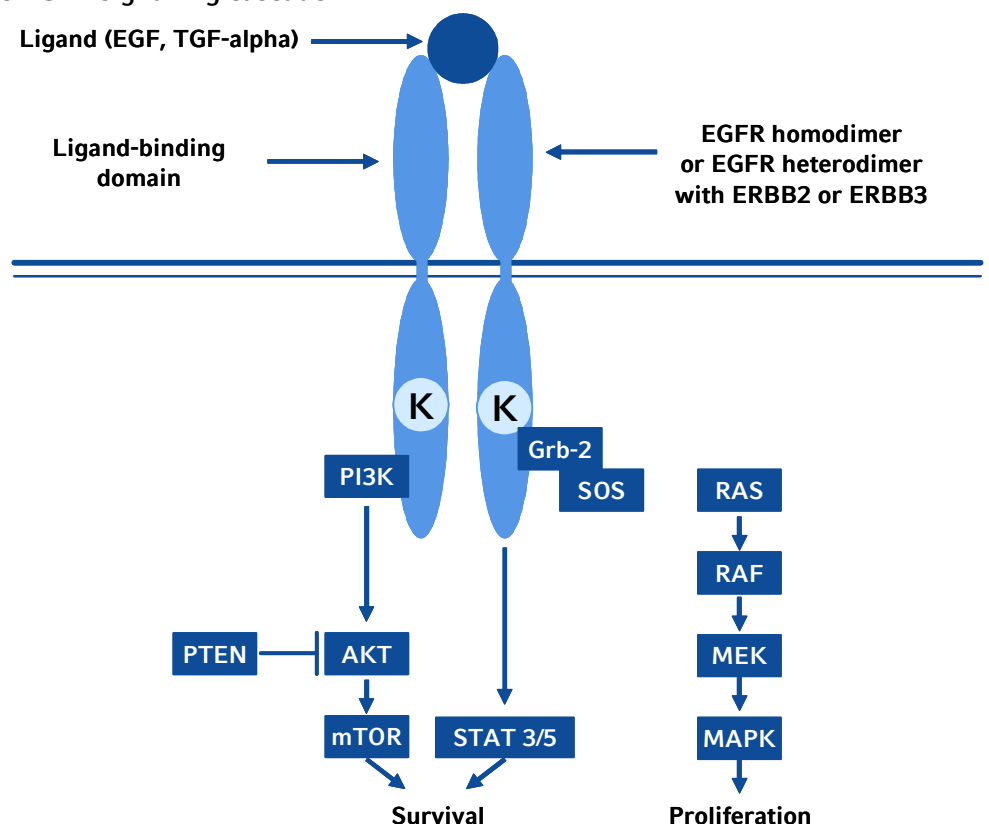
Vectibix was initially not approved in Europe

Vectibix had initially not achieved regulatory approval in Europe in refractory mCRC. In its rejection of the application for marketing authorisation, the EU's Committee for Medicinal Products for Human Use (CHMP) criticised the design of the Phase III study and Vectibix's failure to increase progression-free survival (PFS) by more than a very small degree, while increasing side-effects (see table 'Vectibix Phase III trial results' below).

KRAS enters the stage

In a subsequent analysis of the trial, Amgen investigated the effect of another biomarker – KRAS – on the efficacy of its drug. KRAS is the human homolog of the **K**irsten **r**at **s**arcoma-2 virus oncogene. It is a signal transducer molecule inside the cell that gets activated through EGFR, and forms part of the signal cascade that eventually results in cell proliferation. KRAS can harbour a number of oncogenic mutations that yield a constitutively active protein, resulting in the proliferation of a cell becoming independent of external stimulus from the EGF receptor.

The EGFR signalling cascade



Source Adapted from Ladanyi and Pao, Modern Pathology 2008

KRAS can be used as a biomarker to predict response to EGFR inhibitors

Mutant KRAS had previously been suggested as being associated with lack of response to EGFR inhibitors such as Vectibix and Erbitux. In the retrospective biomarker analysis of its Phase III trial, Amgen showed that it was indeed only patients with the KRAS wild-type version who benefited from treatment with Vectibix, and that PFS in KRAS wild-type

patients treated with Vectibix was substantially higher (12.3 weeks) than across the whole patient pool treated with Vectibix (8 weeks; see table below).

Vectibix Phase III trial results

	No. of patients	PFS (weeks)	Response rate (%)
Best supportive care (BSC), all patients	232	7.3	0
Vectibix, all patients	231	8.0	10
Vectibix, KRAS WT patients	124	12.3	17
Vectibix, KRAS mutant patients	84	7.4	0

Source Amgen, WestLB Research estimates

Vectibix gained European approval in KRAS wild-type patients

Based on these new data, Amgen received European regulatory approval for Vectibix for the treatment of mCRC in patients harbouring the KRAS wild-type gene whose disease has progressed after standard chemotherapy regimens.

Erbix efficacy in first-line mCRC is dependent on KRAS status

It was not surprising that, as for Vectibix, Erbitux efficacy turned out to be coupled to KRAS status. In the Phase III Crystal trial, only those patients who had the KRAS wild-type gene benefited from treatment with Erbitux, while patients with mutant KRAS did not.

Erbitux Crystal Phase III trial results

Patient subpopulation	Median PFS (months) chemo + mAB	Median PFS (months) chemo + placebo	Hazard ratio	Median OS (months) chemo + mAb	Median OS (months) chemo + placebo	Hazard ratio	Response rate chemo + mAb	Response rate chemo + placebo
KRAS wild-type	9.9	8.7	0.68	24.9	21.0	0.840	59%	43%
KRAS mutant	7.6	8.1	1.07	17.5	17.7	1.030	n/a	n/a

Source Merck KGaA, WestLB Research estimates

Erbitux in mCRC is approved in Europe for patients with KRAS WT status only

Based on these data and data from the Phase II CELIM study, Erbitux was approved in Europe for the first-line treatment of patients with mCRC harbouring the wild-type version of KRAS. At the same time, the existing approval for Erbitux in second and further lines of mCRC was amended to include the KRAS label. To date, Imclone/BMS have not submitted an application to the FDA for first-line use of Erbitux in mCRC, and hence the drug is not approved in the USA in this indication, nor does it have the KRAS label there.

The first-line label has the potential to more than make up for the KRAS restriction

This label extension in Europe was generally viewed by the market as a bit of a double-edged sword. On the one hand, Merck had enlarged Erbitux' target population significantly by getting Erbitux approved in first-line mCRC, while at the same time 40% of previously eligible second- and further-line patients were excluded from treatment with Erbitux (see table below). However, as the first-line population is not only more numerous but is also, on average, treated for a longer period, the KRAS wild-type population alone offers more annual treatment weeks (number of patients x average treatment duration) than second- and third-line including KRAS mutants. Despite the KRAS cut, including first-line patients looks distinctly like a very attractive move to us.

Potential annual treatment weeks for Erbitux in mCRC

	1 st line patients	2 nd line patients	3 rd line patients	2 nd and 3 rd line combined
Total patient population	87,950	37,800	11,300	49,100
KRAS WT (60%)	52,770	22,680	6,780	29,460
KRAS mutant (40%)	35,180	15,120	4,520	19,640
Treatment duration (weeks)	32	20	16	n/a
Annual treatment weeks total patient population	2,814,400	756,000	180,800	936,800
Annual treatment weeks KRAS WT	1,688,640	453,600	108,480	562,080

Source Merck KGaA, WestLB Research

The label change initially affected Erbitux growth negatively

Sales of Erbitux in second and further lines of mCRC were initially hit, as KRAS testing had previously not been done routinely and there was some confusion amongst clinicians on how to implement such testing into the work-up of patients. As a result, sales of Erbitux did not reach Merck's target of €600m (\$882m) in Europe and Japan in 2008. As Merck has since started pushing Erbitux in combination with a KRAS test, Erbitux is now back on its growth path. We estimate the hit in second and further lines due to the KRAS label will be more than compensated for by sales in first-line mCRC.

Sales of Vectibix have disappointed so far but not due to KRAS

Sales of Vectibix have disappointed so far. However, this is due not to KRAS but to Vectibix only getting approval for third and further lines of treatment, as the trial investigating Vectibix in combination with Avastin in first-line mCRC failed. This has seriously limited Vectibix' potential in the mCRC indication, as third and further lines account for only a small fraction of the overall patient pool. However, Vectibix' fate may be about to turn, as results from two Phase III studies without Avastin in first- and second-line mCRC have shown that Vectibix in addition to standard chemotherapy does indeed prolong progression-free survival and increases objective response rates (ORR). Although the data, particularly in terms of ORR in first-line treatment, were not as good as some may have hoped, Vectibix may yet take off.

Sales of Erbitux and Vectibix

Sales (\$m)	2001	2002	2003	2004	2005	2006	2007	2008	2001-08 CAGR %
Erbitux (total)	0	0	0	366	710	1,114	1,336	1,592	44.4
Erbitux (Merck only)	0	0	0	105	297	462	644	843	68.3
Vectibix	0	0	0	0	0	39	170	153	98.1

Source Amgen, Merck KGaA, WestLB Research

Resurrecting Iressa

For AstraZeneca the value of a theranostics-based approach was recently evident with the positive Interest trial data of its once doomed NSCLC therapy Iressa. The product was initially granted accelerated FDA approval after encouraging IDEAL data, but when the ISEL data showed that no significant improvement could be achieved with the drug, European marketing approval was withdrawn and major US label changes were swiftly made. However, a specific mutation to EGFR affecting a proportion of NSCLC patients, notably Asians, women and non-smokers, was subsequently identified. This, and the availability of a diagnostic test (Genzyme), enabled Astra to carry out a large-scale Phase III biomarker programme, with the results proving the significant benefit of the drug to a subgroup of NSCLC patients.

What's in the pipeline?

We have analysed the pipelines of the seven European pharmaceutical companies in our coverage universe by presence or absence of an associated biomarker programme. We have found that although all have biomarker research to some extent, the difference between the various companies' approaches is huge, from 100% of Roche's pipeline projects having an associated biomarker programme to <1% of Bayer's.

Most pharmaceutical companies do not publicise which of their pipeline projects have an associated biomarker programme. Hence, our data was collected by trawling through a number of databases and industry reports, discussing with company representatives and attending conferences, and we cannot dismiss the possibility that we have missed the odd biomarker programme. Furthermore, for our analysis we have included any biomarker programme, i.e. for patient stratification and where biomarkers are used as surrogates or to measure treatment success during treatment.

Roche is ahead

Roche is furthest advanced

Roche is well ahead with its approach to drug-associated biomarker research; all its pipeline projects have associated biomarker programmes in accordance with an internal policy that has been in place since the beginning of the year. Roche benefits here from its own diagnostics unit, which facilitates involving diagnostics in the drug development process from the very beginning, without having to worry about confidentiality issues.

The experience with Erbitux gives Merck a head start

The company with the next-highest percentage of biomarker programmes for its pipeline projects is Merck KGaA, with 64%. Unlike Roche, Merck does not have its own diagnostics division. However, its experience with Erbitux is likely to have alerted it to the benefits of biomarkers early on, and has given it a head start over most other competitors.

Novartis is trying to catch up

Although not as far advanced, Novartis is catching up, with 39% of all pipeline projects having an associated biomarker programme. As well as stepping up its efforts on the biomarker front, the company founded an MDx unit within its oncology group at the beginning of 2009, with the initial aim of identifying biomarkers for oncology pipeline projects.

GSK is incorporating biomarker identification studies into some late-stage trials

Whilst not having a biomarker programme for every pipeline project, GSK has recently begun to incorporate biomarker identification studies into a number of its late-stage clinical trials. In terms of pipeline opportunities, we regard the MAGE-A3 based, antigen-specific cancer immunotherapeutics programme as an exciting opportunity for the development of NSCLC and melanoma targeted therapies, whilst a collaboration with OncoMethylone Sciences is actively looking into a handful of undisclosed targets for cancer therapy. Finally, in the event that darapladib successfully negotiates clinical development and becomes approved, GSK has plans to develop a Lp-PLA2 companion diagnostics test.

Not many biomarker programmes at Astra, but personalised medicine is core component of R&D strategy

Personalised medicine remains a core component of Astra’s R&D strategy, owing in part to its experiences with Iressa. The development of the PARP inhibitor Olaparib was aided by the identification of BRCA mutations, and the HDAC inhibitor AZD9468 is currently being investigated under collaboration utilising a biomarker platform. Away from oncology, the company aims to drive additional growth from its Crestor franchise with a label extension and companion diagnostic test for C-reactive protein.

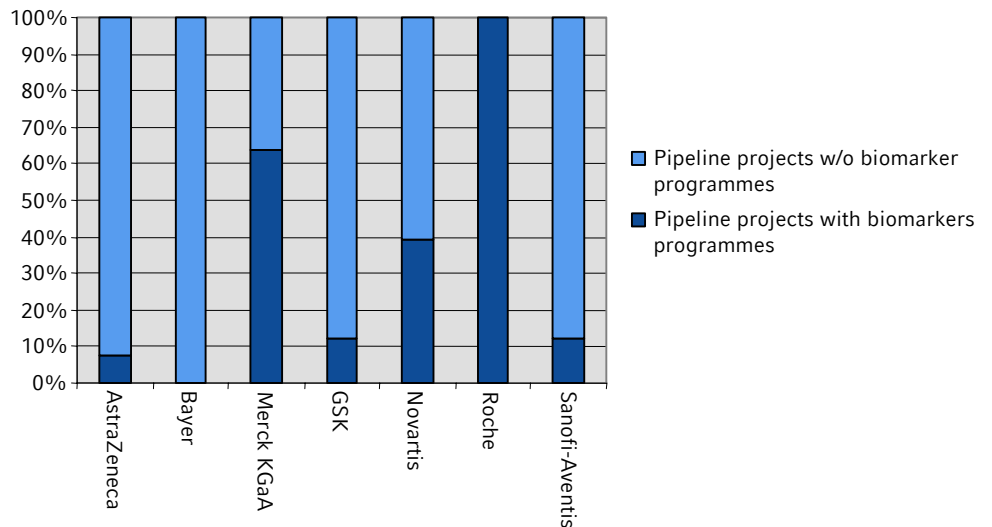
Sanofi-Aventis is currently a lagger but its approach may be about to turn

Sanofi-Aventis is a lagger in embracing biomarkers within its clinical development work. But with recent management changes the company is undergoing a strategic overhaul that includes the R&D division. Consequently we would not be surprised to see in the near future a more determined approach to biomarkers in order to participate in ‘niche’ busters.

No focus on developing biomarkers at Bayer

Bayer does not put much emphasis on the discovery and development of biomarkers. Although Bayer routinely studies biomarkers during early drug development stages to better characterise patients, these studies are usually not geared towards finding stratification or safety markers.

Pipeline projects by presence or absence of biomarker programme



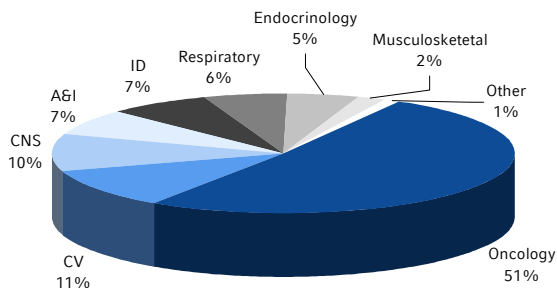
Source Companies, WestLB Research estimates

Oncology leads

Oncology accounts for 51% of all biomarker programmes

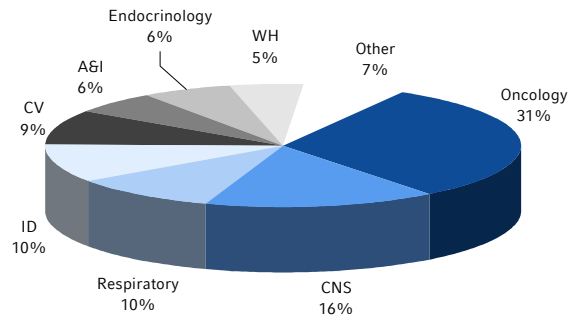
Oncology is the clear leader in terms of therapy area, with 51% of all biomarker programmes attached to oncology drug development projects. The dominance of oncology projects by biomarker programmes can partly be explained by the fact that oncology projects account for the largest chunk (31%) of all pipeline projects we have identified for the seven companies we have studied for this report. However, we believe there are other factors that can explain the focus of biomarker discovery on oncology projects.

Pipeline projects with biomarker by therapy area



Source Companies, WestLB Research estimates

Total pipeline projects by therapy area



Source Companies, WestLB Research estimates

It may be relatively easy to identify a biomarker for an oncology drug

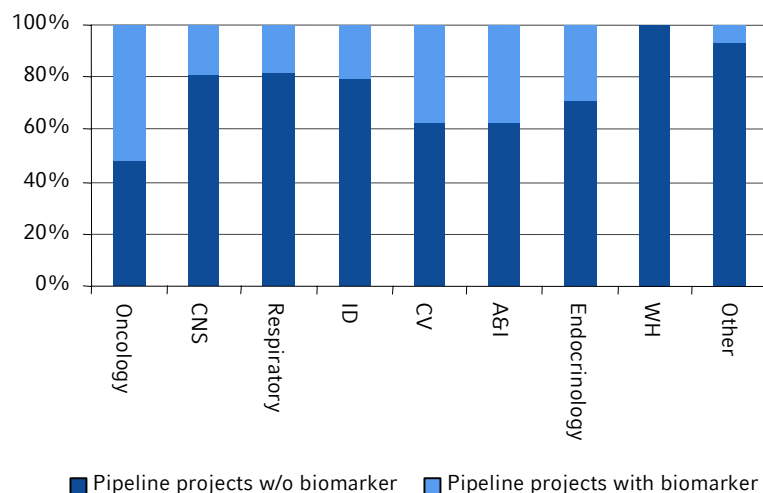
A large proportion of oncology drugs are targeted therapies that interfere with a single molecule that often feeds into a well defined signalling cascade. Identifying a biomarker for a targeted therapy is thus – at least in theory – relatively easy. Should the target molecule not be present in a patient (e.g. HER2 for Herceptin or EGFR for Erbitux or Vectibix), the targeted drug is not going to work in this particular patient, and a biomarker has been found. Equally, if a mutation renders a molecule in the signalling cascade downstream of the target molecule independent from an activating signal from that target molecule, blocking the target molecule will not result in the desired blockage of that signalling cascade; hence the drug is useless in patients with this mutation (e.g. KRAS for Erbitux).

Furthermore, novel oncology drugs tend to be highly priced, and patient stratification for the Phase III trial may help to show the benefit to justify those high prices.

No other therapy area dominates the remaining 49% of biomarker programmes.

The fraction of projects with biomarker programmes within each therapy area highlights again that the effort to identify biomarkers is most pronounced in oncology, with c. 52% of projects having an associated biomarker programme. Other areas that have a high percentage of biomarker programmes are cardiovascular (CV, 38%) and autoimmune and inflammatory diseases (AGI, 37%).

Fraction of pipeline projects by presence or absence of biomarker



Source Companies, WestLB Research estimates

Small molecules rather than antibodies dominate

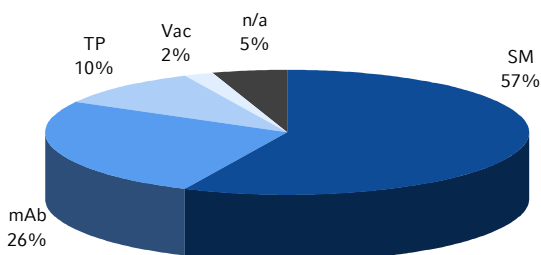
We had envisaged the focus to be on mAbs, but SMs actually dominate

Small molecules (SMs) account for 57% of pipeline projects with an associated biomarker programme, while monoclonal antibodies (mAbs) account for only 26%. Initially we found this result surprising, as we were expecting mAbs to dominate biomarker research. As all mAbs are targeted therapies and hence influence only a single molecule, we argued that it should be crucial to identify patients in whom the antibody cannot work because of a mutation in the target or one of its downstream effector molecules. It should also be easier than for SMs, which often target several molecules at once (e.g. multi-kinase inhibitors).

However, a look at the overall pipeline shows that this is likely to be a reflection of the dominance by SMs of the overall pipelines, where they account for 62% of projects. On the other hand, the percentage of mAbs in the pipeline with associated biomarker programme (26%) is disproportionately higher than the percentage of mAbs in the overall pipeline (14%). This clearly indicates that there is a focus on mAbs in biomarker research.

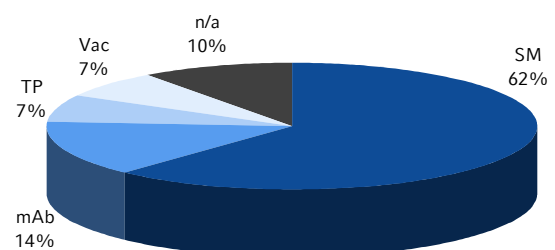
Targeted proteins and vaccines account for only small percentages of all biomarker programmes (10% and 2% respectively).

Pipeline projects with biomarker programmes, by molecule type



Source Companies, WestLB Research estimates

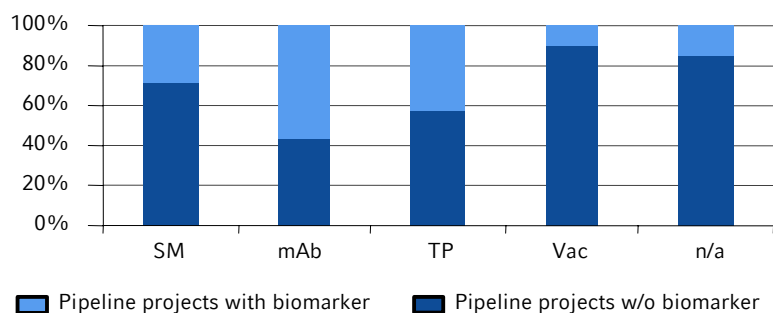
Total pipeline projects, by molecule type



Source Companies, WestLB Research estimates

Looking at the fraction of projects with biomarker programmes within each molecule class shows clearly that the greatest effort to identify biomarkers is being made for mAbs, with 57% of all projects in this molecule class having an associated biomarker project. There also appears to be a lot of effort devoted to identifying biomarkers for therapeutic proteins (TPs), with 43% of all pipeline projects with a biomarker programme.

Fraction of pipeline projects with biomarker programmes, by molecule type



Source Companies, WestLB Research estimates

Company profiles

25 September 2009

AstraZeneca

REDUCE

Current price 2745.0p

Target price 2700.0p

Pan European Equity
UKLife Sciences
Pharmaceuticals

Focus on personalised oncology

Personalised medicine remains a core component of AstraZeneca's oncology R&D strategy, owing in part to its mixed first-hand experiences with Iressa. Identification of VEGF/EGFR mutation may yet still prove important to the eventual success of Zactima and Recentin, with late-stage clinical trials of both products still progressing. In the earlier-stage setting, the identification of BRCA1 & BRAC2 mutations have lent to the development of the PARP inhibitor Olaparib, in addition to the HDAC inhibitor AZD9468, which is currently being investigated utilising a biomarker platform. Away from the field of oncology, the company's interest in biomarkers remains high on the agenda, with the potential CRP label extension to Crestor following the JUPITER data and a number of smaller collaborations. Astra is clearly not a fully integrated molecular diagnostics player, but the company remains committed to the field of personalised medicine, and sees its potential for renewed innovation in the area of research and development.

Year end	Sales	EBT	EPS	P/E	EV/EBITDA	EV/EBIT	Yield
Dec	(\$m)	(\$m)	(\$)	(x)	(x)	(x)	(%)
2008A	31,600	8,680	4.20	9.6	5.9	6.9	4.7
2009E	31,931	10,492	5.07	8.7	5.3	5.9	4.6
2010E	31,231	9,677	4.69	9.4	5.3	6.1	4.9
2011E	29,880	9,353	4.53	9.7	5.2	6.4	4.6

Source AstraZeneca, WestLB Research estimates

Resurrecting Iressa

AstraZeneca's mixed recent experience with Iressa clearly demonstrates the potential value of theranostics in aiding new product development and, in the event of unexpected hurdles, in breathing new life into what would otherwise be an overlooked therapeutic opportunity. Iressa was initially granted accelerated FDA approval for sufferers of NSCLC who had failed two prior chemotherapy courses on the basis of promising early Ideal study data. The drug suffered a significant setback, however, with the release of Phase III ISEL data that failed to show any significant improvement in overall survival associated with administration of the drug. This led to an enforced change to the US label and the subsequent withdrawal of the European marketing application. Despite the negative data it was clear that in a number of patients, especially those of Asian origin, a significant benefit could be seen, but not until the responsible mutations to EGFR could be identified could any reason behind the efficacy discrepancies be explained.

Key data

in %	1m	3m	12m
Absolute	-2.6	1.7	11.6
Relative	-3.9	-12.6	23.5

12 month price range 2947.00p - 2075.00p

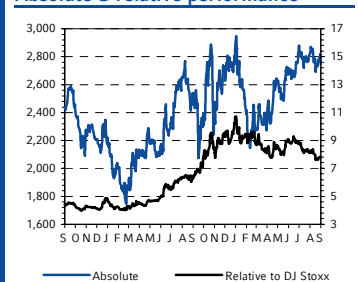
Net cash/share YE	-\$3.7
NAV/share YE	\$14.1
No. shares in issue	1452.0m
Free float	100.0%
Market cap	£39,857m
Next event	Q3 Result
Date	29/10/2009
Reuters code	AZN.L
Bloomberg code	AZN LN
DJ Stoxx	239.98

Unless otherwise stated, share prices are as of market close on the business day before the date of the report

Extra-Financial Rating

Environment	A+	Governance	A+
Social	A+	Risk Discount	5.5%

Absolute & relative performance



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As a result of the findings, Astra embarked on a large-scale Phase III biomarker-linked clinical programme, with the recent positive outcome of the Interest trial paving the way for European marketing approval. Thus, without the knowledge gained from the targeted theranostic approach Iressa would have gone down as another one of the many failures in late-stage pharmaceutical product development. With the availability of a diagnostic test by Genzyme, however, patients can now be screened for the mutation to help identify those patients who could benefit from Iressa therapy.

Focus on oncology

Owing in part to the aforementioned mixed fortunes with Iressa, biomarker-led personalised medicine is now a core component of AstraZeneca's oncology R&D strategy. Mixed data have already been reported for the Phase III pipeline products Zactima and Recentin, and we cannot yet rule out the prospect that various mutations to VEGF or EGFR will play an important role in the overall commercial success of the products. In a similar manner the theranostics-based approach, via the identification of BRCA-1 & 2 mutations, has lent itself to the development of the Phase II PARP inhibitor Olaparib, with a much earlier-stage product, the histone deacetylase inhibitor AZD 9468, currently under development in a partnership with Celleron Therapeutics. The product is being developed in conjunction with Celleron's proprietary CancerNav predictive biomarker platform, which identifies those tumours most likely to respond to individual drugs, i.e. a closely linked diagnostic and therapeutic diagnostic approach.

CRP: potential to drive Crestor growth

Away from oncology, an area where AstraZeneca hope to gain added benefit from the theranostics approach in the near future is via the pending label extension of Crestor to cover patients with elevated CRP levels. The Jupiter study's identification that patients with elevated CRP can benefit from Crestor treatment leads to the possibility of a companion diagnostic test, to identify those patients who do not currently qualify for statin treatment (presenting with normal cholesterol levels) and who would benefit from such therapeutic intervention.

'Hair-brained' ideas

Other collaborations in the field of biomarkers and theranostics of which AstraZeneca is currently part include a project with Epistem and an ongoing investigation with the Banner Alzheimer's Institute. Utilising the knowhow and technology of Epistem, Astra aims to steer oncology drug development using biomarker profiling of the human hair, whereby gene expression profiling of RNA from bulb cells located at the base of individual hairs can be achieved. Research into the ability for early diagnosis of Alzheimer's disease has been carried out with the Banner Institute, with the development of the PET radioligand [18F]-AZD4694, which binds to amyloid plaques in the brain – a hallmark of Alzheimer's disease. AstraZeneca hopes that this technology will aid the future discovery of treatments for Alzheimer's through continued development.

Investment case

The emerging field of theranostics has clearly aided AstraZeneca in recent months, with the resurrection of the once ill-fated NSCLC drug Iressa. Moreover, a number of earlier-stage projects, whilst not openly highlighting the company's utilisation of the technology, have clearly benefited from the approach, and the company is potentially set to reap the rewards once again with the opportunity to extend a CRP label to Crestor in the coming

months. Despite AstraZeneca's involvement in theranostics, the next few years look to us particularly tough for the company. We forecast negative sales and earnings growth with the loss of patent protection to a number of products including Arimidex and Seroquel, declining sales of Nexium in the USA, and potential concerns over the Crestor patent situation expected to take centre stage from early 2010. Astra has had a good run of late, driven by positive pipeline developments with Onglyza and – more recently – Brilinta, in addition to aggressive restructuring benefits. Questions remain, however, as to whether this is sustainable, and we believe investors are likely to focus on the negatives of this undiversified company in the coming months, with its relatively thin late-stage pipeline, excess exposure to the US primary care markets, and uncertainties over a number of product franchises. We therefore lower our recommendation to Reduce (was Neutral) and set our new 12-month price target at £27.00.

AstraZeneca P&L (\$m)

Year ending December	2008A	2009E	2010E	2011E	2012E	2013E	CAGR 08-13E
Group sales	31,600	31,931	31,231	29,880	29,363	29,404	-1.4%
<i>Change y-o-y (%)</i>	6.9	1.0	-2.2	-4.3	-1.7	0.1	
Cost of goods sold	-6,598	-5,988	-6,090	-5,827	-6,020	-6,028	
<i>% of sales</i>	20.9	18.8	-19.5	-19.5	-20.5	-20.5	
Gross profit	25,002	25,943	25,141	24,053	23,344	23,376	-1.3%
<i>% of sales</i>	79.1	81.2	80.5	80.5	79.5	79.5	
Selling, general & administrative expenses	-10,913	-10,694	-10,462	-10,010	-9,837	-9,850	
<i>% of sales</i>	34.5	33.5	-33.5	-33.5	-33.5	-33.5	
Research & development expenses	-5,179	-4,628	-4,997	-4,781	-4,698	-4,705	
<i>% of sales</i>	16.4	14.5	-16.0	-16.0	-16.0	-16.0	
Other operating income/expenses	524	904	625	598	587	588	
<i>% of sales</i>	1.7	2.8	2.0	2.0	2.0	2.0	
Operating income (EBIT)	9,143	11,245	10,025	9,561	9,102	9,115	-0.1%
<i>EBIT margin (%)</i>	28.9	35.2	32.1	32.0	31.0	31.0	
Depreciation/amortisation	2,620	1,741	2,196	2,196	2,196	2,196	
EBITDA	11,763	12,986	12,221	11,757	11,298	11,311	-0.8%
<i>EBITDA margin (%)</i>	37.2	40.7	39.1	39.3	38.5	38.5	
Interest income/expenses	-463	-753	-348	-208	-84	40	
Others	0	0	0	0	0	0	
Earnings before taxes (EBT)	8,680	10,492	9,677	9,353	9,018	9,155	1.1%
<i>Pre-tax margin (%)</i>	27.5	32.9	31.0	31.3	30.7	31.1	
Income taxes	-2,551	-3,129	-2,855	-2,759	-2,660	-2,701	
<i>Tax rate (%)</i>	-29.4	-29.8	-29.5	-29.5	-29.5	-29.5	
Net profit (before minorities)	6,129	7,362	6,822	6,594	6,358	6,454	1.0%
<i>ROS (%)</i>	19.4	23.1	21.8	22.1	21.7	22.0	
Minorities	-32	-29	-24	-32	-32	-32	
Net profit (after minorities)	6,100	7,338	6,790	6,562	6,326	6,422	1.0%
<i>% change y-o-y</i>	9.0	20.3	-7.5	-3.4	-3.6	1.5	
Reported EPS	4.20	5.07	4.69	4.53	4.37	4.44	1.1%
<i>% change y-o-y</i>	12.2	20.7	-7.5	-3.4	-3.6	1.5	
Restructuring charges plus	1,407	1,090	1,126	574	564	564	
MedImmune/Merck amortisation							
Core EPS (€)	5.10	5.62	5.27	4.84	4.67	4.74	-1.5%
<i>% change y-o-y</i>	16.3	10.3	-6.3	-8.1	-3.5	1.4	

Source Company, WestLB Research estimates

25 September 2009

Bayer

ADD
 Current price €46.2
 Target price €52.0

Pan European Equity
 Germany
Life Sciences
Speciality Pharmaceuticals

Theranostics not in focus

Theranostics is not a major focus for Bayer. Looking at pipeline projects, we have identified some biomarker programmes for Nexavar, and biomarkers are routinely studied in the early drug development stages for patient characterisation but mostly not with a view of using such biomarkers for the purpose of stratification. Bayer's focus on specialty pharma and small molecules rather than antibodies may mean that biomarkers are not as crucial for them now. However, if regulators and payers really push stratified medicine, Bayer may have to review its standpoint.

Year end	Sales	EBT	EPS	P/E	EV/EBITDA	EV/EBIT	Yield
Dec	(€m)	(€m)	(€)	(x)	(x)	(x)	(%)
2008A	32,918	2,356	4.17	10.0	7.1	11.3	3.4
2009E	31,327	3,006	4.05	11.4	7.6	12.7	3.1
2010E	32,808	4,461	4.94	9.4	7.0	10.4	3.7
2011E	34,190	4,816	5.24	8.8	6.3	9.2	4.0

Source Bayer, WestLB Research estimates

No theranostics exposure

Bayer does not have a drug with a companion diagnostic on the market and of the seven pharmaceutical companies analysed in this report, Bayer has the lowest percentage of pipeline projects with biomarker programmes. There are a number of ongoing trials with Nexavar that evaluate whether there are any biomarkers that could predict outcome or that would allow monitoring of treatment success.

Although clinicaltrials.gov lists several trials conducted by Bayer for a number of compounds other than Nexavar, Bayer makes it clear that these are routine patient and drug characterisations, rather than a search for a marker that could later on be used as companion diagnostic.

Examples of pipeline projects with biomarker programmes

Drug	Drug type	TA	Indication	Status	Biomarker
BAY 80-6946	n/a	Oncology	Solid tumours	I	✓
DAST Inhibitor (Bay 73-4506)	SM	Oncology	Solid tumours	I	✓
Nexavar	SM	Oncology	Solid tumours	III/II	✓

Source WestLB Research, Company

Key data

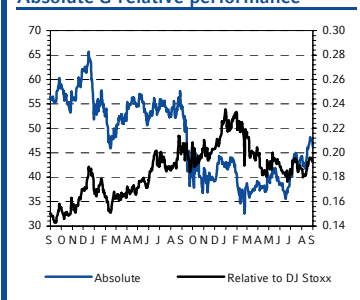
in %	1m	3m	12m
Absolute	4.3	18.8	-14.8
Relative	2.9	2.1	-5.7
12 month price range	€54.42 - €32.69		
Net cash/share YE	-€14.1		
NAV/share YE	€22.6		
No. shares in issue	824.0m		
Free float	100.0%		
Market cap	€38,052m		
Next event	Q3 Result		
Date	27/10/2009		
Reuters code	BAYGn.DE		
Bloomberg code	BAY GR		
DJ Stoxx	239.98		

Unless otherwise stated, share prices are as of market close on the business day before the date of the report

Extra Financial-Rating

	A+	Governance	A-
Environment	A	Risk Discount	B
Social			#####

Absolute & relative performance



Research analyst

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Most currently available theranostics are in oncology. Although one of Bayer's growth drivers is an oncology drug – Nexavar – its presence in the oncology market has so far been limited. With its focus on primary care, women's health and specialty pharmaceuticals, Bayer may not have felt the need to invest heavily in biomarker research. However, if Bayer wants to expand its presence in the oncology sector (and looking at the pipeline, this is a sector it is targeting), and if regulators and payers are going to put increasing emphasis on a drug's cost-benefit and risk-benefit profile, it may have to reassess its position. In fact, it may already have recognised this, given the number of currently ongoing trials including biomarker analyses for stratification purposes for Nexavar.

Investment case

After Material Science had an abysmal start to the year with underlying EBITDA margin plunging into negative territory (-9.2%), the unit seems to have managed a turn around in Q2. We expect a continued albeit slow recovery over the remainder of 2009 with sales of the unit down 19.5% yoy and underlying EBITDA margin inching up towards the 4% mark for the whole year. Growth is likely to be held back by material prices rising higher but we believe this could be compensated for by a continued trend of increasing selling prices. Bayer Healthcare offers a pipeline rich in newsflow over the next 12 months which may well contribute to driving the share price. As valuations for chemicals and consumer healthcare peers have come up over the past few months, our SOTP model now points to a fair value of €52 per share, which we adopt as our new price target.

Bayer P&L

(€m)	2008A	2009E	2010E	2011E	2012E	2013E
Sales						
HealthCare	15,407	16,056	16,744	17,207	17,561	18,082
CropSciences	6,382	6,631	6,843	7,016	7,131	7,208
MaterialSciences	9,738	7,422	7,851	8,597	9,149	9,382
Reconciliation	1,391	1,218	1,370	1,370	1,370	1,370
Group sales	32,918	31,327	32,808	34,190	35,211	36,042
% growth yoy	1.6	-4.8	4.7	4.2	3.0	2.4
COGS	-16,456	-15,062	-15,846	-16,514	-17,007	-17,408
Gross profit	16,462	16,265	16,962	17,676	18,204	18,634
margin (%)	50.0	51.9	51.7	51.7	51.7	51.7
Selling costs	-8,105	-7,779	-8,136	-8,445	-8,662	-8,830
R&D costs	-2,653	-2,708	-2,768	-2,783	-2,817	-2,883
G&A costs	-1,649	-1,562	-848	-884	-910	-932
Other operating income	907	546	0	0	0	0
Other operating expenses	-1,418	-757	0	0	0	0
EBIT	3,544	4,006	5,209	5,564	5,815	5,988
margin (%)	21.5	24.6	30.7	31.5	31.9	32.1
Underlying core EBITDA						
BHC	4,157	4,481	4,581	4,711	4,810	4,959
BCS	1,603	1,671	1,711	1,754	1,783	1,802
BMS	1,088	258	499	653	881	1,093
Reconciliation	83	105	100	100	100	100
Underlying EBITDA group	6,931	6,515	6,891	7,219	7,573	7,954
Underlying EBITDA margin (%)	21.1	20.8	21.0	21.1	21.5	22.1
Non-operating result	-1,188	-1,000	-748	-748	-748	-748
EBT	2,356	3,006	4,461	4,816	5,067	5,240
Taxes	-636	-905	-1,338	-1,445	-1,520	-1,572
tax rate (%)	-27.0	-30.1	-30.0	-30.0	-30.0	-30.0
Net income (continuing business)	1,720	2,100	3,123	3,371	3,547	3,668
% growth yoy	-25.4	22.1	48.7	8.0	5.2	3.4
Financing expenses for mand. conv.	112	51	0	0	0	0
Adjusted net income	1,832	2,151	3,123	3,371	3,547	3,668
Number of ordinary shares	824	824	824	824	824	824
EPS (diluted), continuing business	2.22	2.55	3.79	4.09	4.30	4.45
% growth yoy	-23.7	17.4	45.2	8.0	5.2	3.4
Reconciliation Core EPS						
EBIT	3,544	4,006	5,209	5,564	5,815	5,988
Amortisation and write-downs intangibles	1,550	1,578	1,600	1,600	1,600	1,600
Write-downs PPE	88	73	50	50	50	50
Special items	665	223	0	0	0	0
Core EBIT	5,847	5,880	6,859	7,214	7,465	7,638
Non-operating result	-1,188	-1,000	-748	-748	-748	-748
Income taxes	-636	-905	-1,338	-1,445	-1,520	-1,572
Tax adjustment	-691	-664	-700	-700	-700	-700
Income after taxes attributable to minority interest	-5	0	-4	-4	-4	-4
Core net income cont. operations	3,327	3,310	4,069	4,317	4,493	4,614
Financing expenses for mand. conv. bond	112	28	0	0	0	0
Adj. core net income	3,439	3,338	4,069	4,317	4,493	4,614
Adjusted weighted average number of shares	824	824	824	824	824	824
Core EPS from cont. operations	4.17	4.05	4.94	5.24	5.45	5.60
% growth yoy	9.7	-2.9	21.9	6.1	4.1	2.7

Source Company, WestLB Research estimates

25 September 2009

GlaxoSmithKline

ADD
 Current price 1206.0p
 Target price 1350.0p

Pan European Equity
 UK

Life Sciences
Pharmaceuticals

Quietly working away

Glaxo, although not as outwardly visible as Roche in MDx, is quietly undertaking a number of steps to expand its exposure in biomarkers, both in patient stratification and in the design of novel targeted therapies. Tykerb is the most obvious licensed product, but investigation into antigen-specific cancer immunotherapeutics and a number of collaborations with external partners highlight the ongoing research in this area. In addition to the early-stage development of a handful of oncology therapies to molecular targets that are as of yet unknown, GSK is currently investigating the potential of an accompanying test for darapladip to measure levels of Lp-PLA2. So although GSK is not adopting a fully integrated approach to MDx, it does not intend to be left behind in this area.

Year end	Sales	EBT	EPS	P/E	EV/EBITDA	EV/EBIT	Yield
Dec	(£m)	(£m)	(p)	(x)	(x)	(x)	(%)
2008A	24,352	6,659	88.62	14.5	9.1	11.1	4.4
2009E	28,608	7,711	105.05	11.5	7.4	8.8	5.1
2010E	29,285	8,317	113.43	10.6	6.8	7.8	5.7
2011E	29,411	8,706	120.84	10.0	6.4	7.4	6.2

Source GlaxoSmithKline, WestLB Research estimates

HER2/neu detection with Tykerb

The most obvious example of GSK's use of theranostics in its product portfolio is the treatment of HER2+ breast cancer with its tyrosine kinase inhibitor Tykerb. Patients overexpressing HER2/neu traditionally present with a more aggressive form of the disease and commonly have a worse prognosis. Through the availability of tests for HER2, studies have found that Tykerb worked best in the 25-30% of patients unfortunate enough to overexpress this gene. They are now offered Tykerb after failure with prior taxane, anthracycline and Herceptin (Roche) therapy. Unlike Herceptin, Tykerb targets the HER2 receptor tyrosine kinase and, due to its small molecular nature, is able to enter cells and inhibit downstream signalling events.

Opportunities in cancer immunotherapeutics

A new approach recently adopted by GSK is the design and development of antigen-specific cancer immunotherapeutics (ASCI), which it hopes will utilise the body's own immune system to combat tumour growth. Specifically, GSK is currently conducting clinical trials in NSCLC (Phase III MAGRIT study) and melanoma (Phase III DERMA study) after the identification of a cancer-specific antigen, MAGE-A3, found to be exclusively expressed in cancer cells (35-50% of patients with NSCLC; 65% of patients with melanoma).

Key data

in %	1m	3m	12m
Absolute	0.3	8.9	1.5
Relative	-1.0	-6.3	12.3

12 month price range 1305.00p - 987.00p

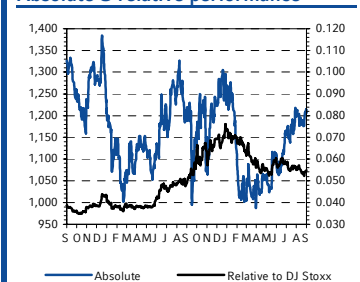
Net cash/share YE	-218.9p
NAV/share YE	197.9p
No. shares in issue	5192.7m
Free float	100.0%
Market cap	£62,624m
Next event	Q3 Result
Date	28/10/2009
Reuters code	GSK.L
Bloomberg code	GSK LN
DJ Stoxx	239.98

Unless otherwise stated, share prices are as of market close on the business day before the date of the report

Extra-Financial Rating

	A+	Governance	A
Environment	A+	Risk Discount	5.0%
Social	A+		

Absolute & relative performance



Research analyst

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GSK believes the ASCI approach elicits a strong immune response against cancer cells with the additional use of GSK's novel adjuvant system. It envisages the methodology having a low side-effect profile and allowing combination treatment with existing therapies, owing to its strong specificity and novel mechanism of action. GSK believes MAGE-A3 is expressed in a number of tumour types, and it is developing a PCR-based molecular diagnostics test through a recently signed collaboration with Abbott Labs, to determine those patients who could benefit from the ASCI therapeutic approach.

Lp-PLA2 companion test for darapladib

Results from the Integrated Biomarkers and Imaging Study-2 (IBIS-2) presented in September 2008 showed that the pipeline product darapladib could lower the activity of the biomarker Lp-PLA2. Lp-PLA2 is an enzyme commonly found in atherosclerotic plaques, with enhanced activity implicated in the development and progression of atherosclerosis often ending in heart attacks and stroke. As a result, and in addition to progressing darapladib into Phase III clinical investigation, GSK is developing an accompanying Lp-PLA2 biomarker test that it hopes will help identify, subsequent to positive trial data and successful marketing approval, those patients who could most benefit from early therapeutic intervention with the drug.

Collaboration with OncoMethylome Sciences for personalised oncology targets

In late 2008 GSK announced its collaboration with the MDx company OncoMethylome Sciences to develop DNA methylation biomarkers for use in the personalisation of cancer treatment. Methylation of DNA regulates gene expression and is commonly associated with cancer development and the response to cancer therapy, with methylation-specific PCR techniques able to detect very early-stage cancer during patient screening. We understand GSK and OncoMethylome Sciences are investigating a handful of targets for undisclosed cancers, with the aim of eventually developing targeted therapies with accompanying molecular diagnostic tests.

Smaller-scale collaboration with Medical Research Council

Moving away from the area of oncology, GSK and the MRC initiated a three-year joint programme in 2008 to identify genes associated with human diseases. Initial projects involved investigation into the molecular basis of depression, obesity and metabolic disorders, with the aim of identifying new targets and biomarkers for the development of novel therapies.

Hypersensitivity to Abacavir

A final area in which GSK relies on a diagnostics-based approach in its current product portfolio is the suitability of its HIV drug Ziagen (abacavir), owing to the occurrence of severe – in some cases fatal – hypersensitivity reactions in a number of patients (5-8%). It has discovered that patients positive for the HLA-B*5701 genetic variation were susceptible to the hypersensitivity reaction. Screening prior to treatment initiation is now recommended, and is routinely carried out.

Investment case

Whilst not adopting a fully integrated approach to MDx, GSK is certainly doing its fair share in this lucrative field, with a number of promising ongoing research projects and collaborations. Since the arrival of Andrew Witty the company has significantly increased its exposure in the lucrative emerging markets, whilst undertaking a large-scale

restructuring programme and, at the same time, reporting some encouraging late-stage pipeline surprises. In acknowledgement of GSK's ever diversifying business model and its emergence from a difficult patent expiry period, in combination with the opportunities offered by swine flu, we set our new price target at £13.50 and reiterate our Add recommendation.

GlaxoSmithKline P&L (£m)

Year ending December	2008A	2009E	2010E	2011E	2012E	2013E	CAGR 08-12E
Group sales	24,352	28,608	29,285	29,411	29,841	30,378	4.5%
<i>Change y-o-y (%)</i>	7	17	2	0	1	2	
Cost of goods sold	-6,415	-7,463	-7,556	-7,529	-7,580	-7,655	
<i>% of sales</i>	26	26	26	26	25	25	
Gross Profit	17,937	21,145	21,730	21,882	22,262	22,723	4.8%
<i>% of sales</i>	74	74	74	74	75	75	
Selling, general & administrative expenses	-7,656	-9,291	-9,225	-9,059	-9,132	-9,357	
<i>% of sales</i>	31	32	32	31	31	31	
Research & development expenses	-3,681	-4,375	-4,393	-4,382	-4,417	-4,435	
<i>% of sales</i>	15	15	15	15	15	15	
Other operating income/expenses	541	761	791	794	806	820	
<i>% of sales</i>	2	3	3	3	3	3	
Operating income (EBIT)	7,141	8,240	8,903	9,235	9,519	9,752	6.4%
<i>EBIT margin (%)</i>	29.3	28.8	30.4	31.4	31.9	32.1	
Depreciation/amortisation	1,543	1,541	1,340	1,340	1,340	1,340	
EBITDA	8,684	9,781	10,243	10,575	10,859	11,092	5.0%
<i>EBITDA margin (%)</i>	35.7	34.2	35.0	36.0	36.4	36.5	
Interest income/expenses	-482	-529	-586	-529	-478	-425	
Earnings before taxes (EBT)	6,659	7,711	8,317	8,706	9,042	9,326	7.0%
<i>Pre-tax margin (%)</i>	27.3	27.0	28.4	29.6	30.3	30.7	
Income taxes	-1,947	-2,273	-2,454	-2,568	-2,667	-2,751	
<i>Tax rate (%)</i>	-29.2	-29.5	-29.5	-29.5	-29.5	-29.5	
Net profit (after minorities)	4,712	5,438	5,864	6,137	6,375	6,575	6.9%
<i>ROS (%)</i>	19	19	20	21	21	22	
<i>% change y-o-y</i>	-12	16	8	5	4	3	
EPS, reported (€)	0.89	1.05	1.13	1.21	1.29	1.37	9.0%
<i>% change y-o-y</i>	-6	19	8	7	7	6	
EPS, core (€)	1.05	1.21	1.23	1.25	1.29	1.37	5.4%
<i>% change y-o-y</i>	6	15	2	2	3	6	

Source Company, WestLB Research estimates

25 September 2009

Merck KGaA

ADD
 Current price €67.4
 Target price €75.0

Pan European Equity
 Germany
Life Sciences
Speciality Pharmaceuticals

A pick and choose approach

Of the seven European pharma companies we have analysed for this report, Merck is the number 2 in terms of percentage of pipeline projects with biomarker programmes (64%). Through its experience with Erbitux, Merck clearly appreciates the benefits biomarkers can offer. Unlike Roche, however, Merck has no diagnostics division, so a shot-gun approach like Roche's, with associated biomarker research for every single pipeline project, is not feasible. Instead, Merck has more of a 'pick and choose' attitude and focuses its biomarker discovery efforts on drug candidates where the mechanism of action suggests particular biomarkers, which is often the case for oncology drugs.

Year end	Sales	EBT	EPS	P/E	EV/EBITDA	EV/EBIT	Yield
Dec	(€m)	(€m)	(€)	(x)	(x)	(x)	(%)
2008A	7,558	1,578	5.72	11.3	7.8	13.9	1.0
2009E	7,674	1,312	4.82	14.0	9.2	18.4	1.1
2010E	8,030	1,679	5.97	11.3	7.1	12.5	1.9
2011E	8,565	1,904	6.86	9.8	6.2	10.2	2.4

Source Merck KGaA, WestLB Research estimates

Experience with Erbitux gives Merck a head start

Through its experience with Erbitux, Merck clearly appreciates the benefits biomarkers can offer, as it was only once KRAS was used as a stratification marker that a statistically significant benefit could be shown in the first-line treatment of metastatic colorectal cancer. It is unlikely that Erbitux would have gained approval in this indication in Europe without KRAS as a biomarker.

So far, however, Merck has been unable to garner the full benefits of stratification biomarkers. The KRAS marker was discovered too late for Merck to benefit from smaller and hence less costly trials.

Merck focuses biomarker programmes on selected projects

Merck is aiming to implement a stratified medicine approach across the whole development portfolio and search for stratification biomarkers during the discovery process. However, unlike Roche, Merck has no diagnostics division and hence involving diagnostics for biomarker research in the very early stages of drug development is likely to be complicated by negotiations with external partners. We thus find it not surprising that Merck has more of a 'pick and choose' attitude and focuses its biomarker discovery efforts on drug candidates where the mechanism of action suggests particular biomarkers, which is often the case for oncology drugs.

Key data

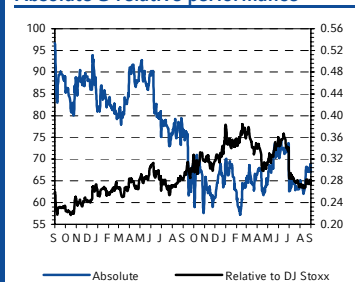
in %	1m	3m	12m
Absolute	5.7	-6.4	-10.4
Relative	4.3	-19.5	-0.8
12 month price range	€76.71 - €57.24		
Net cash/share YE	-€6.0		
NAV/share YE	€44.1		
No. shares in issue	217.4m		
Free float	27.8%		
Market cap	€14,657m		
Next event	Q3 Result		
Date	26/10/2009		
Reuters code	MRCG.F		
Bloomberg code	MRK GR		
DJ Stoxx	239.98		

Unless otherwise stated, share prices are as of market close on the business day before the date of the report

Extra Financial-Rating

	B-	Governance	D
Environment	B-	Risk	6.5%
Social	B-	Discount	

Absolute & relative performance

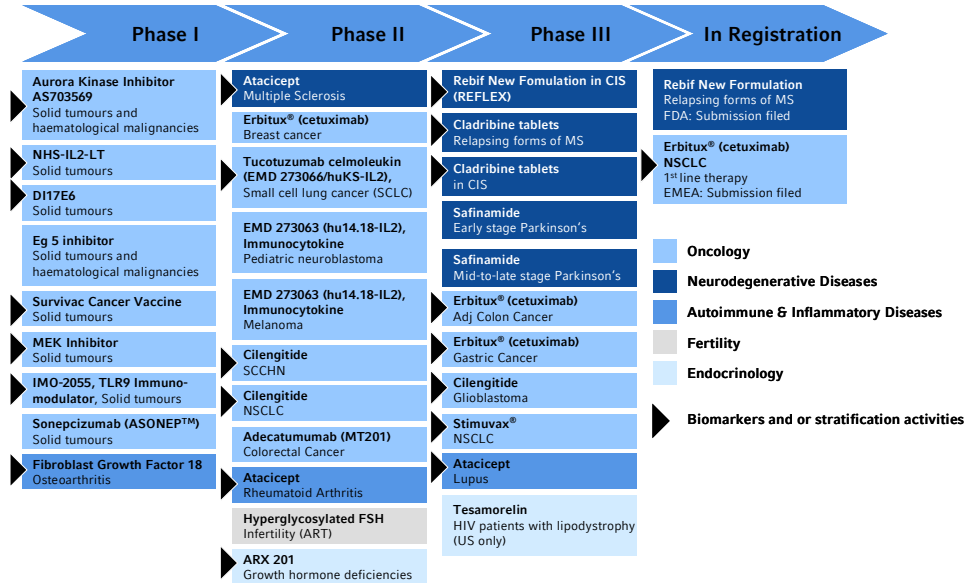


Source JCF, WestLB Research, Asset4

Research analyst

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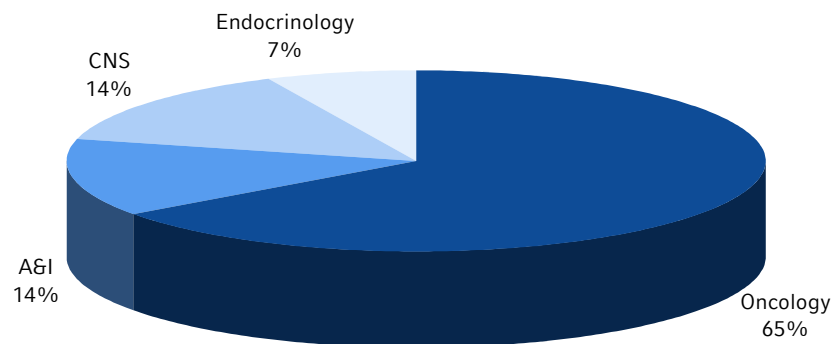
Merck Serono's pipeline contains many projects with biomarker programmes



Source Company, WestLB Research

Consequently, the vast majority (65%) of Merck's biomarker programmes is focused on oncology drug projects (n.b. if a drug is in development in several indications in the same therapy area, we have only counted it once for that therapy area).

Biomarker programmes by therapeutic area



Source Company, WestLB Research

One example from Merck's pipeline of an oncology drug with associated biomarker programme is Cilengitide which is currently in a Phase III trial in glioblastoma (a type of brain cancer). In a number of Phase II trials Merck is investigating whether the methylation status of the MGMT gene promoter can be used as a stratification marker. As with Erbix, the biomarker appears not to have been discovered until relatively late during the development process as patients in the ongoing Phase III trial have been recruited regardless of the status of their MGMT promoter. Hence, Merck is again missing out on the full benefits a biomarker could offer during drug development.

Investment case

Taking into account the continued strong recovery of the LCD panel market, we believe that management's 2009 guidance for the LC business of a drop in revenues of 20-25% is too cautious. Our model which takes into account most recent worldwide sales of LCD panels points towards a decline in revenues of 12.5% for Merck's LC unit. On the pharma side, we believe that recently presented data at the European oncology meeting

ECCO/ESMO - while not presenting the additional upside that may have been hoped for - should support Erbitux on its growth path. Given the upside we see in LCs for 2009, and which consensus does not appreciate yet, and the better outlook for Erbitux, we have an Add rating with a target price of €75 on the stock.

Merck KGaA P&L

(€m)	2008A	2009E	2010E	2011E	2012E	2013E	2014E
Group sales	7,558	7,674	8,030	8,565	9,033	9,094	9,238
<i>% change y-o-y</i>	7.1	1.5	4.6	6.7	5.5	0.7	1.6
Cost of sales	-1,906	-1,995	-2,128	-2,235	-2,323	-2,312	-2,313
<i>% of sales</i>	-25.2	-26.0	-26.5	-26.1	-25.7	-25.4	-25.0
Gross profit	5,652	5,680	5,902	6,330	6,710	6,782	6,925
<i>Gross margin (%)</i>	74.8	74.0	73.5	73.9	74.3	74.6	75.0
Marketing and selling expenses	-2,097	-2,249	-2,216	-2,355	-2,475	-2,464	-2,504
<i>% of sales</i>	-27.7	-27.7	-27.6	-27.5	-27.4	-27.1	-27.1
Administration expenses	-446	-442	-490	-521	-547	-555	-562
<i>% of sales</i>	-5.9	-6.2	-6.1	-6.1	-6.1	-6.1	-6.1
Research and development	-1,234	-1,327	-1,379	-1,412	-1,436	-1,448	-1,475
<i>% of sales</i>	-16.3	-17.3	-17.2	-16.5	-15.9	-15.9	-16.0
Goodwill amortization	-574	-577	-592	-610	-628	-647	-666
Operating result	1,131	866	1,225	1,432	1,624	1,668	1,718
<i>Operating margin (%)</i>	15.0	11.3	15.3	16.7	18.0	18.3	18.6
Core operating result	1,735	1,443	1,555	1,777	1,919	1,960	2,024
<i>Core operating margin (%)</i>	22.9	18.8	19.4	20.7	21.2	21.6	21.9
EBIT	731	797	1,225	1,432	1,624	1,668	1,718
<i>EBIT margin (%)</i>	9.7	10.4	5.3	16.7	18.0	18.3	18.6
Financial result	-156	-131	-138	-138	-138	-138	-138
Earnings before taxes (EBT)	574	666	1,087	1,294	1,486	1,530	1,580
<i>Pretax margin (%)</i>	7.6	8.7	13.5	15.1	16.5	16.8	17.1
Adjusted EBT	1,578	1,312	1,679	1,904	2,114	2,177	2,246
Income taxes	-196	-187	-272	-323	-372	-383	-395
<i>Tax rate (%)</i>	-34.1	-28.1	-25.0	-25.0	-25.0	-25.0	-25.0
Net profit (before minorities)	379	478	815	971	1,114	1,147	1,185
<i>ROS (%)</i>	5.0	6.2	10.2	11.3	12.3	12.6	12.8
Minorities	-13	-4.95	-10	-10	-10	-10	-10
Net profit (after minorities)	366	474	805	961	1,104	1,137	1,175
<i>% change y-o-y</i>	na	29.5	70.1	19.3	14.9	3.0	3.3
No. of shares (m)	217.4	217.4	217.4	217.4	217.4	217.4	217.4
EPS	1.69	2.18	3.71	4.42	5.08	5.23	5.41
<i>% change y-o-y</i>	0.0	28.8	70.1	19.3	14.9	3.0	3.3
Core EPS	5.72	4.82	5.97	6.86	7.60	7.84	8.10
<i>% change y-o-y</i>	9.9	-15.7	23.8	14.9	10.8	3.1	3.4

Source Company, WestLB Research estimates

25 September 2009

Novartis

ADD

Current price CHF 50.2

Target price CHF 58.0

Pan European Equity
Switzerland

Life Sciences

Pharmaceuticals

Jumping on the bandwagon

Novartis founded a MDx unit within its oncology group at the beginning of 2009 with the initial aim of identifying biomarkers for oncology pipeline projects. Eventually, this MDx group is also supposed to collaborate with other units on biomarker programmes but for the time being the focus is clearly on oncology. Although not as far advanced as Roche in its theranostics approach, Novartis is clearly trying to catch up and hence stands a chance to benefit from theranostics as well.

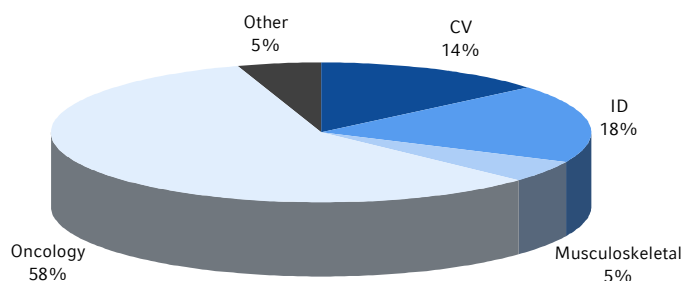
Year end Dec	Sales (\$m)	EBT (\$m)	EPS (\$)	P/E (x)	EV/EBITDA (x)	EV/EBIT (x)	Yield (%)
2008A	42,584	9,499	3.59	13.8	10.1	13.2	3.7
2009E	42,778	9,665	3.91	12.5	9.8	12.1	4.2
2010E	44,921	10,360	4.42	11.0	9.1	11.3	4.4
2011E	46,265	10,715	4.30	11.4	8.9	11.0	4.3

Source Novartis, WestLB Research estimates

Initial focus on oncology

We have identified 21 pipeline projects in Novartis pipeline which appear to have an associated biomarker programme. As one might expect given that the molecular diagnostics group is focusing initially on Novartis' oncology group, the majority of these projects (58%) are in an oncology indication.

Pipeline projects with biomarker programmes by therapy area



Source Company, WestLB Research

The number of pipeline projects with biomarker programmes is likely to increase over the next few years as the new MDx unit gets into full swing. We anticipate that oncology will remain the sector with most biomarker programmes for the foreseeable future. However, as time moves on and the MDx unit gets more established, we are likely to see an increase in the percentage of biomarker programmes in other therapy areas

Key data

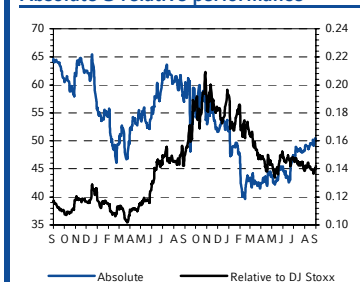
in %	1m	3m	12m
Absolute	3.9	10.3	-14.3
Relative	2.6	-5.2	-5.2
12 month price range	61.15 - 39.64		
Net cash/share YE	\$0.1		
NAV/share YE	\$21.3		
No. shares in issue	2342.0m		
Free float	100.0%		
Market cap	CHF117,451m		
Next event	Q3 Result		
Date	22/10/2009		
Reuters code	NOVN.VX		
Bloomberg code	NOVN VX		
DJ Stoxx	239.98		

Unless otherwise stated, share prices are as of market close on the business day before the date of the report

Extra Financial-Rating

	A-	A
Environment	A-	A
Social	A-	A
Governance	A-	A
Risk Discount	5.0%	

Absolute & relative performance



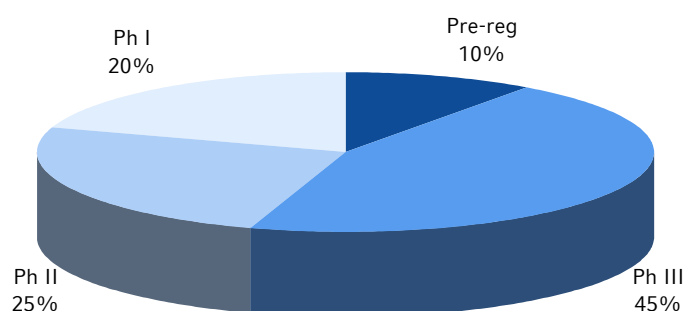
Research analyst

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Focus currently on late-stage projects

The majority of Novartis' pipeline projects with biomarker programmes are in Phase III clinical development, suggesting that so far, there has not been much emphasis on co-developing a biomarker from early development stages onward. Biomarker programmes so far appear to have been an afterthought. However, in this respect too, the new MDx unit could result in a paradigm shift, and a more systematic approach to biomarkers may result in more drug candidates having an associated biomarker programme from early development stages onwards.

Pipeline projects with biomarker programme by status



Source Company, WestLB Research

While not as far advanced as Roche in its drive to identify biomarkers for new drug projects, Novartis appears to have jumped on the bandwagon now. The creation of its own MDx unit should give Novartis an edge over competitors who do not have in-house MDx expertise as we believe in-house expertise is going to be crucial in driving a theranostics approach forward.

Examples of pipeline drugs with biomarker programme for potential stratification

Drug	Therapy area	Indication	Molecule type	Status
ACZ885 (Ilaris)	A&I	Refractory gout, SJIA, RA, T2D	mAb	Ph III/II
SBR759	Other	Hyperphosphatemia	other	Ph II
RAF265	Oncology	Melanoma	SM	Ph I
RAD001 (Afinitor, everolimus)	Oncology	Solid and haematological tumours	SM	Pr-reg/ Ph III
LBH589 (panobinostat)	Oncology	Haematological/solid tumours	SM	various, incl. Ph III
EPO906 (patupilone)	Oncology	Ovarian cancer, solid tumours	SM	Ph III, II

Source Company, WestLB Research estimates

Investment case

As we believe that there are various potential near-term catalysts for the share price (pivotal Phase III data for the multiple sclerosis product FTY720, pandemic vaccines and the generic Lovenox opportunity) we upgrade Novartis from neutral to Add, with a DCF-based target price of CHF 58. While we acknowledge that there is still a patent cliff ahead, Novartis has successfully managed to accelerate volume and the organic revenue growth rate in H1 this year. Thus we expect business at Sandoz and the vaccines & diagnostics division to improve further giving some upside to earnings estimates in 2010 and beyond.

Novartis revenue forecast by indication area

US\$m	2008A	2009E	2010E	2011E	2012E	2013E	CAGR '09-'13E
Cardiovascular/metabolism	8,183	8,642	9,130	9,233	8,435	6,092	-8.4
% change y-o-y	10.5	5.6	5.6	1.1	-8.6	-27.8	
Oncology	8,211	8,716	9,326	9,420	9,450	9,214	1.4
% change y-o-y	18.1	6.2	7.0	1.0	0.3	-2.5	
Neuroscience & Ophthalmics	4,605	4,604	4,724	4,838	4,982	5,120	2.7
% change y-o-y	5.9	0.0	2.6	2.4	3.0	2.8	
Respiratory	1,084	1,113	1,161	1,216	1,271	1,326	4.5
% change y-o-y	13.0	2.7	4.3	4.7	4.5	4.3	
Immunology and Infectious Diseases	2,954	2,877	3,140	3,465	3,772	4,054	9.0
% change y-o-y	-1.3	-2.6	9.1	10.4	8.9	7.5	
Other additional mature products	1,294	1,507	1,453	1,413	1,382	1,360	-2.5
% change y-o-y	-5.5	16.5	-3.6	-2.8	-2.2	-1.6	
Total prescription drug sales	26,331	27,459	28,934	29,585	29,292	27,166	-0.3
% change y-o-y	9.6	4.3	5.4	2.2	-1.0	-7.3	

Source Company, WestLB Research estimates

Novartis profit & loss forecasts

US\$m	2008A	2009E	2010E	2011E	2012E	2013E	CAGR '09-'13E
Net sales	41,459	41,967	44,091	45,435	45,871	44,511	
% change y-o-y	8.9	1.2	5.1	3.0	1.0	-3.0	
Other sales	1,125	811	830	830	830	830	
% change y-o-y	28.6	-27.9	2.3	0.0	0.0	0.0	
Group sales	42,584	42,778	44,921	46,265	46,701	45,341	1.5
% change y-o-y	9.3	0.5	5.0	3.0	0.9	-2.9	
Cost of goods sold	-11,439	-11,362	-11,888	-12,294	-12,690	-12,736	
% of revenues	-26.9	-26.6	-26.5	-26.6	-27.2	-28.1	
Gross profit	31,145	31,416	33,033	33,971	34,011	32,605	
Gross margin (%)	73.1	73.4	73.5	73.4	72.8	71.9	
Marketing & sales	-11,852	-11,695	-12,279	-12,619	-12,744	-12,267	
% of revenues	-27.8	-27.3	-27.3	-27.3	-27.3	-27.1	
General & administration	-2,245	-2,221	-2,291	-2,351	-2,389	-2,372	
% of revenues	-5.3	-5.2	-5.1	-5.1	-5.1	-5.2	
Research & development	-7,217	-7,307	-7,580	-7,781	-7,787	-7,415	
% of revenues	-16.9	-17.1	-16.9	-16.8	-16.7	-16.4	
Other income & expenses	-867	-736	-763	-785	-796	-783	
Operating income	8,964	9,457	10,120	10,435	10,295	9,768	0.8
Operating margin (%)	21.1	22.1	22.5	22.6	22.0	21.5	
EBITDA	11,724	11,741	12,549	12,923	12,843	12,372	1.3
EBITDA margin (%)	27.5	27.4	27.9	27.9	27.5	27.3	
Financial result	535	208	240	280	310	640	
Earnings before taxes (EBT)	9,499	9,665	10,360	10,715	10,605	10,408	1.9
Pre-tax margin (%)	22.3	22.6	23.1	23.2	22.7	23.0	
Income taxes	-1,336	-1,409	-1,502	-1,554	-1,538	-1,509	
Tax rate (%)	-14.1	-14.6	-14.5	-14.5	-14.5	-14.5	
Net profit (before minorities) from cont.	8,163	8,256	8,858	9,161	9,067	8,899	1.9
ROS (%)	19.2	19.3	19.7	19.8	19.4	19.6	

Source Company, WestLB Research estimates

25 September 2009

Qiagen

ADD
 Current price €14.3
 Target price €15.8

Pan European Equity
 Netherlands
 Life Sciences
 Medical Technology

In an excellent position

We believe Qiagen is well positioned to benefit from increasing emphasis on theranostics. The majority of emerging biomarkers is likely to require MDx testing, and Qiagen is a major player in the MDx arena. Going forward, Qiagen's emphasis is on building its MDx franchise with a focus on personalised medicine, which the company perceives as a high-growth, high-margin area. We cannot rule out a possible takeover of Qiagen, but we question how attractive Qiagen's remaining business would be for a pharma player.

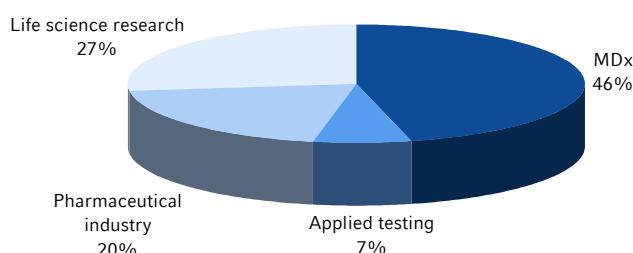
Year end	Sales (\$m)	EBT (\$m)	EPS (\$)	P/E (x)	EV/EBITDA (x)	EV/EBIT (x)	Yield (%)
2008A	893	226	0.80	21.6	11.6	16.5	0.0
2009E	969	261	0.90	23.5	12.0	17.0	0.0
2010E	1,086	316	1.00	21.1	11.3	15.6	0.0
2011E	1,214	363	1.15	18.3	10.1	13.7	0.0

Source Qiagen, WestLB Research estimates

Well positioned in the MDx arena

Qiagen identified the molecular diagnostics (MDx) market as a major growth area. It spotted the opportunity it had in the MDx market through its expertise in the laboratory consumables and instruments space, but it also realised that organic growth alone would not be sufficient to catapult it into the MDx premier league. Qiagen had always counted diagnostics laboratories amongst its customers for its consumables, but it truly entered the market for MDx test kits in 2005 when it bought artus GmbH. Qiagen finally achieved the desired step change from laboratory consumables supplier to major MDx player, with its acquisition of Digene with its HPV test in July 2007. In 2008 the MDx franchise accounted for revenues of \$435m (c. 46% of its total revenues), which would make Qiagen now the No. 2 player in MDx. The recent acquisition of DxS, a pioneer in the area of companion diagnostics should help Qiagen maintain that position and expand its market share.

Qiagen – revenues by business area, 2008



Source WestLB Research estimates

Key data

in %	1m	3m	12m
Absolute	-2.7	11.5	6.9
Relative	-3.9	-4.1	18.3

12 month price range €15.67 - €10.19

Net cash/share YE -\$1.4

NAV/share YE \$8.7

No. shares in issue 234.5m

Free float 87.0%

Market cap €3,358m

Next event Q3 Result

Date 09/11/2009

Reuters code QGEN.F

Bloomberg code QIA GR

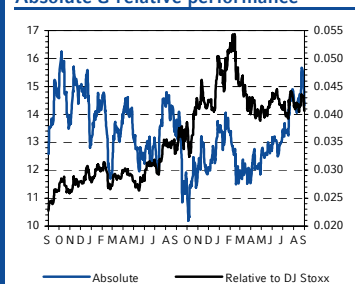
DJ Stoxx 239.98

Unless otherwise stated, share prices are as of market close on the business day before the date of the report

Extra-Financial Rating

Environment	D	Governance	A-
Social	C+	Risk Discount	4.5%

Absolute & relative performance



Research analysts

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MDx likely to play a major role in theranostics

It is possible that some biomarkers emerging as companion diagnostics are going to be physiological (e.g. blood pressure) or imaging markers (detected in *in vivo* tests). However, we envisage that a large proportion will be of a molecular nature (i.e. mutations in or methylation status of a gene, presence/absence of a particular protein) and will require molecular *in vitro* testing.

With the DxS acquisition announced last week, Qiagen is expanding its already substantial offerings in companion diagnostics such as the PyroMark KRAS test (predicts response to Erbitux and Vectibix) and the Olerup SSP HLA-B*5701 test (predicts whether an AIDS patient is likely to develop a hypersensitivity reaction to treatment with Abacavir) by 7 further tests targeting biomarkers and a near-term pipeline containing 10 further assays. In addition, Qiagen is co-developing further companion diagnostics with 15 pharmaceutical partners.

MDx likely to remain a growth driver for Qiagen

Qiagen's proprietary pyrosequencing technology is particularly well suited to companion diagnostics, as it allows the detection of changes in the DNA at several positions in a single reaction, something not achievable with regular PCR. This technology thus has the potential to speed up testing, which would be highly desirable when a fast decision regarding which drug to give to a patient is required. We thus expect the list of Qiagen's companion diagnostics to expand significantly over the next few years.

Unlikely takeover candidate

We acknowledge that Qiagen's MDx segment is likely to attract some attention from pharmaceutical companies seeking to gain or expand expertise in MDx. However, we think Qiagen is an unlikely takeover target, as we question the attractiveness of its consumables business to pharmaceutical companies. Qiagen lab consumables are used throughout academia and the life sciences industry. Actually owning the lab consumables business may not be of particular interest to any one pharmaceutical company, but no pharmaceutical company is likely to want that business in the hands of a competitor. The fear of sparking a bidding war may well put off potential suitors for Qiagen.

But likely to remain an active acquirer

With the acquisition of DxS, Qiagen also announced issuance of 27.5m new shares. However, Qiagen could easily have financed the DxS takeover without this capital increase. The money raised has likely been earmarked for further acquisitions in the personalised healthcare space to enable Qiagen to pounce quickly if suitable and attractive opportunity arises.

Investment case

Qiagen used to be a supplier of lab consumables to academia and industry. However, in recent years the company has increased its focus on the fast-growing MDx market, where it now occupies the no. 2 spot behind Roche Diagnostics. In addition, it develops and markets its own instruments, which run with Qiagen consumables only, thus tying the customer into Qiagen's products. The company has convinced in recent years with steadily increasing earnings. Qiagen's MDx segment is currently growing at around 20%. With our forecast of 14% CAGR for the MDx market from 2008 to 2013, and Qiagen's excellent position within this market, we are forecasting the segment to remain a major growth driver over the next few years. Our DCF-based valuation indicates a fair value of €15.8 per share.

Qiagen P&L

(€m)	2008A	2009E	2010E	2011E	2012E	2013E
Total revenues	893.0	969.4	1086.4	1214.2	1353.0	1502.4
<i>% change y-o-y</i>	37.4	8.6	12.1	11.8	11.4	11.0
Cost of goods sold	-293.3	-326.4	-327.5	-354.8	-383.6	-413.6
<i>% of revenues</i>	-32.8	-33.7	-30.1	-29.2	-28.4	-27.5
Gross profit (reported)	599.7	643.0	758.9	859.4	969.4	1088.8
<i>Gross margin (%)</i>	67.2	66.3	69.9	70.8	71.6	72.5
Sales and marketing	-227.4	-237.1	-262.5	-289.7	-318.8	-349.5
<i>% of revenues</i>	-25.5	-24.5	-24.2	-23.9	-23.6	-23.3
General and administrative, integration and others	-113.9	-104.4	-114.8	-125.9	-137.6	-149.8
<i>% of revenues</i>	-12.8	-10.8	-10.6	-10.4	-10.2	-10.0
Research and development	-97.3	-105.0	-108.1	-121.4	-135.3	-150.2
<i>% of revenues</i>	-10.9	-10.8	-10.0	-10.0	-10.0	-10.0
Acquisition related intangible amortization		-15.7	-17.4	-19.4	-21.6	-24.0
<i>% of revenues</i>		-1.6	-1.6	-1.6	-1.6	-1.6
Purchased in-process research and development	-1.0	-5.0	0.0	0.0	0.0	0.0
<i>% of revenues</i>	-0.1	-0.5	0.0	0.0	0.0	0.0
EBIT (reported)	145.7	180.8	256.1	302.9	356.1	415.3
<i>EBIT margin (%)</i>	16.3	18.7	23.6	25.0	26.3	27.6
Adjustments	107.0	97.9	80.0	80.0	80.0	80.0
EBIT (adjusted)	252.7	278.7	336.1	382.9	436.1	495.3
<i>EBIT (adjusted) margin (%)</i>	28.3	28.8	30.9	31.5	32.2	33.0
Other (expense) income, net	1.6	4.6	1.1	1.1	1.1	1.1
Financial result	-28.0	-24.9	-21.0	-21.0	-21.0	-21.0
Earnings before taxes (EBT)	119.3	160.6	236.2	283.0	336.2	395.4
<i>Pretax margin (%)</i>	13.4	34.6	21.7	23.3	24.8	26.3
Income taxes	-29.8	-38.1	-54.9	-65.2	-76.7	-89.4
<i>Tax rate (%)</i>	-24.9	-23.7	-23.2	-23.0	-22.8	-22.6
Net profit (bef. minorities) continuing	89.5	122.5	181.3	217.8	259.5	306.0
Minorities	-0.5	0.0	0.0	0.0	0.0	0.0
Net profit (aft. minorities) continuing	89.0	122.5	181.3	217.8	259.5	306.0
<i>% change y-o-y</i>	77.5	37.6	48.1	20.1	19.1	17.9
Total no. of shares (m)	204.3	211.9	234.5	236.5	238.5	240.5
Diluted net (loss) income per share	0.44	0.58	0.77	0.92	1.09	1.27
Net Earnings calculation incl adjustments						
Earnings before taxes (EBT)	119.3	160.6	236.2	283.0	336.2	395.4
Adjustments	107.0	100.6	80.0	80.0	80.0	80.0
Earnings before taxes (EBT) before exceptionals	226.3	261.2	316.2	363.0	416.2	475.4
Income taxes before exceptionals	-62.9	-71.2	-82.2	-91.5	-95.0	-107.5
<i>Tax rate (%)</i>	-27.8	-27.3	-26.0	-25.2	-22.8	-22.6
Net profit	163.3	190.0	234.0	271.5	321.2	367.9
<i>% change y-o-y</i>	46.6	16.3	23.2	16.0	18.3	14.5
Total no. of shares (m)	204.3	211.9	234.5	236.5	238.5	240.5
Adjusted, diluted net (loss) income per share	0.80	0.90	1.00	1.15	1.35	1.53
<i>% change y-o-y</i>	25.9	12.5	11.3	15.1	17.3	13.6

Source Company, WestLB Research estimates

25 September 2009

Roche

ADD

Current price CHF 167.0

Target price CHF 185.0

Pan European Equity
Switzerland

Life Sciences

Pharmaceuticals

Best in class

Personalised Health Care is a big buzzword at Roche and in fact, no other large-cap pharma company is probably as well positioned as Roche to drive this approach forward. Its established and integrated diagnostics business, including MDx, should guarantee a smoother development process for theranostics than could be achieved with an outside partner. In addition, Roche already has experience in marketing theranostics products through Herceptin. We hence forecast that Roche is likely to benefit most from the increased focus on cost-benefit ratio adopted by healthcare systems.

Year end Dec	Sales (CHFm)	EBT (CHFm)	EPS (CHF)	P/E (x)	EV/EBITDA (x)	EV/EBIT (x)	Yield (%)
2008A	45,617	14,161	10.40	15.6	7.3	8.7	2.6
2009E	49,076	11,821	9.74	17.2	6.3	7.5	2.8
2010E	49,265	14,649	11.43	14.6	5.8	6.9	3.1
2011E	51,766	15,895	12.51	13.3	5.0	5.9	3.4

Source Roche, WestLB Research estimates

Roche is way ahead of competitors in terms of personalised healthcare

Over the past year, Roche has established guidelines for personalised healthcare which stipulate that every pipeline project should have an associated biomarker programme. It is unlikely that every such project will come up with a biomarker for a compound. Biomarkers emerging from these programmes are likely to be used eventually for patient stratification as well as therapeutic monitoring. This policy clearly shows Roche's commitment to this approach and its conviction that theranostics does not only have the potential to benefit the patient but also the pharma company.

Through its diagnostics division, Roche can run an integrated theranostics approach. This has the advantage of cutting out any outside party which would necessitate more administration work e.g. confidentiality agreements. In our view such an integrated approach has the advantage of cutting down administration and negotiation time and cost and ensuring complete confidentiality, as no information on pipeline projects is circulated outside Roche. Furthermore, it facilitates involving diagnostics from very early development stages onwards.

Roche has a head start in terms of marketing theranostics

The experience gathered with Herceptin gives Roche a head start in terms of marketing know how of such products. In addition, we believe that this experience in combination with its presence in the diagnostics space gives it the necessary clout to push the combination of a drug with companion diagnostics into both doctors' practices and diagnostics labs at the same time.

Key data

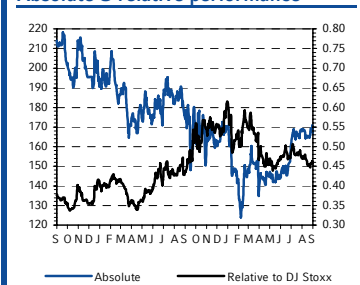
in %	1m	3m	12m
Absolute	-0.5	14.8	-4.3
Relative	-1.8	-1.3	5.9
12 month price range	181.10 - 124.10		
Net cash/share YE	CHF31.5		
NAV/share YE	CHF67.0		
No. shares in issue	860.0m		
Free float	100.0%		
Market cap	CHF143,620m		
Next event	Q3 sales		
Date	15/10/2009		
Reuters code	ROG.VX		
Bloomberg code	ROG.VX		
DJ Stoxx	239.98		

Unless otherwise stated, share prices are as of market close on the business day before the date of the report

Extra Financial-Rating

	A	B
Environment	A+	Governance
Social	A+	Risk Discount 2.5%

Absolute & relative performance



Source JCF, WestLB Research, Asset4

Research analyst

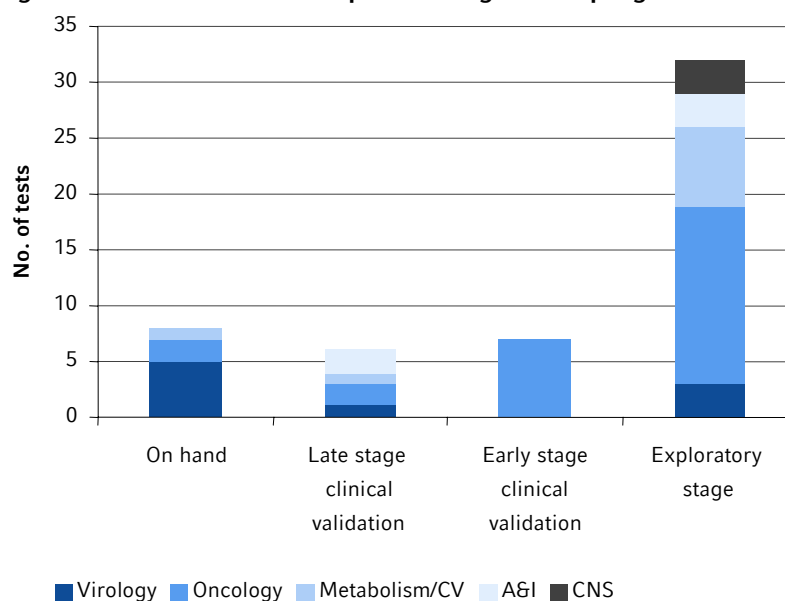
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Looking at theranostics from a diagnostics angle, Roche already markets a number of companion diagnostics, particularly in the virology area where viral load is used to determine whether a therapy has eliminated an infection or whether it is necessary to continue treatment.

Oncology companion diagnostics gaining in importance

There are a total of 45 companion diagnostics tests in the pipeline. While the majority of tests at hand are in the virology area, an increasing emphasis on oncology is discernible in the pipeline, with 56% of all pipeline projects targeting this area.

Roche diagnostics – Formalised companion diagnostics programmes



Source Company, WestLB Research

Investment case

After a difficult start to 2009, management was able to give a more upbeat assessment of 2009 and 2010 upon closing of the Genentech transaction. Moreover we expect more newsflow catalysts for the remainder of the year and at least three filings for new products in 2010. Thus, with a limited exposure to patent expiries and virtually sheltered (due to its oncology portfolio accounting for more than 50% of sales) from price pressure, we expect ongoing above-peer-group EPS growth rates in the coming years. In addition, further demand into 2010 for its antiviral Tamiflu might lead to higher than currently guided sales for the product of CHF400m in 2010. Thus given the company's solid growth profile we upgrade the shares to an Add with a CHF 185 target price.

Roche pharmaceuticals sales forecast by indication area

CHFm	2008A	2009E	2010E	2011E	2012E	2013E	CAGR '09-'13E
Oncology	19,654	21,681	23,575	25,846	27,888	29,758	8.2
% change y-o-y	7.6	10.3	8.7	9.6	7.9	6.7	
Inflammation/Autoimmune/Transplantation	3,264	2,909	2,605	2,546	2,581	2,643	-2.4
% change y-o-y	10.4	-10.9	-10.5	-2.3	1.4	2.4	
Virology	3,408	4,913	3,462	3,614	3,758	3,901	-5.6
% change y-o-y	-31.9	44.2	-29.5	4.4	4.0	3.8	
Metabolism/Bone	2,839	2,808	2,674	2,580	2,502	1,900	-9.3
% change y-o-y	0.7	-1.1	-4.8	-3.5	-3.0	-24.1	
Renal anemia	1,318	1,369	1,360	1,386	1,408	1,397	0.5
% change y-o-y	-13.3	3.9	-0.7	1.9	1.6	-0.8	
Others	5,478	5,495	5,500	5,506	5,512	5,518	0.1
% change y-o-y	-12.0	0.3	0.1	0.1	0.1	0.1	
Total pharmaceutical sales	35,961	39,175	39,176	41,478	43,649	45,117	3.6
% change y-o-y	-2.2	8.9	0.0	5.9	5.2	3.4	

Source Company, WestLB Research estimates

Roche profit & loss forecasts

CHFm	2008A	2009E	2010E	2011E	2012E	2013E	CAGR '09-'13E
Group sales	45,617	49,076	49,265	51,766	54,147	55,837	3.3
% change y-o-y	-1.1	7.6	0.4	5.1	4.6	3.1	
Cost of goods sold	-13,661	-14,568	-14,542	-15,203	-15,838	-16,307	
% of revenues	-29.9	-29.7	-29.5	-29.4	-29.3	-29.2	
Gross profit	31,956	34,508	34,723	36,563	38,309	39,530	3.5
Gross margin (%)	70.1	70.3	70.5	70.6	70.7	70.8	
Marketing & distribution	-9,170	-9,430	-9,495	-9,955	-10,395	-10,711	
% of revenues	-20.1	-19.2	-19.3	-19.2	-19.2	-19.2	
General & administration	-2,332	-2,180	-2,201	-2,309	-2,411	-2,488	
% of revenues	-5.1	-4.4	-4.5	-4.5	-4.5	-4.5	
Research & development	-8,845	-9,494	-9,628	-10,154	-10,653	-10,998	
% of revenues	-19.4	-19.3	-19.5	-19.6	-19.7	-19.7	
Royalties & other operating income	2,287	2,251	2,250	2,250	2,250	2,250	
Operating income	13,896	15,655	15,649	16,395	17,100	17,583	2.9
Operating margin (%)	30.5	31.9	31.8	31.7	31.6	31.5	
Exceptionals	28	-2,363	0	0	0	0	
EBIT	13,924	13,292	15,649	16,395	17,100	17,583	7.2
EBIT margin (%)	30.5	27.1	31.8	31.7	31.6	31.5	
EBITDA	16,673	18,430	18,424	19,170	19,875	20,358	2.5
EBITDA margin (%)	36.5	37.6	37.4	37.0	36.7	36.5	
Financial result	237	-1,471	-1,000	-500	-250	200	
Earnings before taxes (EBT)	14,161	11,821	14,649	15,895	16,850	17,783	10.7
Pretax margin (%)	31.0	24.1	29.7	30.7	31.1	31.8	
Income taxes	-3,317	-2,280	-3,662	-3,974	-4,213	-4,446	
Tax rate (%)	-23.4	-19.3	-25.0	-25.0	-25.0	-25.0	
Net profit (before minorities)	10,844	10,844	9,541	10,987	11,921	12,637	3.9
ROS (%)	23.8	23.8	19.4	22.3	23.0	23.3	
Minority interest	-1,875	-1,158	-1,150	-1,150	-1,150	-1,150	
Net profit (after minorities)	8,969	8,383	9,837	10,771	11,487	12,187	9.8

Source Company, WestLB Research estimates

25 September 2009

Sanofi-Aventis

NEUTRAL

Current price €50.1

Target price n/a

Pan European Equity
France**Life Sciences**
Pharmaceuticals

Time will tell

Sanofi-Aventis is a clear lagger in embracing personalized medicine with regard to actively utilizing biomarkers in clinical trials. The reason might be that in the past the company was focusing less on targeted therapies and more on small molecule drugs developed for blockbuster indications. But with the new management on board Sanofi-Aventis might take a more considered view in the evaluation of future R&D projects and consequently might also embark on an R&D approach which would include personalized medicine.

Year end	Sales	EBT	EPS	P/E	EV/EBITDA	EV/EBIT	Yield
Dec	(€m)	(€m)	(€)	(x)	(x)	(x)	(%)
2008A	28,817	8,952	5.40	8.4	6.5	6.8	4.7
2009E	29,605	8,925	5.14	9.8	6.7	6.9	4.6
2010E	29,865	10,565	6.42	7.8	6.2	6.4	4.8
2011E	30,640	10,812	6.68	7.5	5.8	6.0	5.1

Source Sanofi-Aventis, WestLB Research estimates

Not actively involved in theranostics – for now

In the past Sanofi-Aventis has not been very much interested in running biomarker programmes in clinical research as the company has focused on trying to create blockbuster products in large patient populations (such as Acomplia in the treatment of metabolic syndrome). Moreover, Sanofi-Aventis is not actively involved in the diagnostics area compared to some of its peers, thus there is no natural interest in embarking on a companion diagnostic based R&D approach. But given that under the new management, Sanofi-Aventis is rigorously reviewing/repositioning its R&D portfolio we would not rule out the possibility of theranostics becoming a topic for Sanofi in the not too distant future.

Broad-based R&D portfolio

Even after the rigorous pipeline review the company has a broad-based R&D portfolio consisting of 34 new molecular entities and 18 vaccines in clinical development. Moreover the company is strengthening its portfolio via acquiring/in-licensing new R&D candidates such as BiPar's PARP inhibitor BSI-201 and Exelixis' oral targeted cancer therapies XL147 and XL765. Still, despite BSI-201 it might still take some time until novel biotech-derived products reach the later stages of clinical development.

Key data

in %	1m	3m	12m
Absolute	5.9	7.6	11.3
Relative	4.6	-7.5	23.2

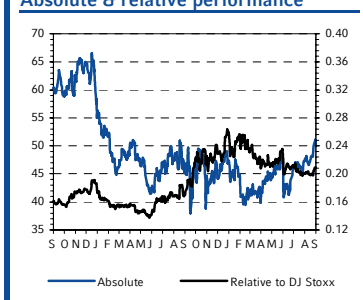
12 month price range	€51.10 - €37.92
Net cash/share YE	-€4.5
NAV/share YE	€39.1
No. shares in issue	1346.9m
Free float	76.2%
Market cap	€67,520m
Next event	Q3 Result
Date	30/10/2009
Reuters code	SASY.PA
Bloomberg code	SAN FP
DJ Stoxx	239.98

Unless otherwise stated, share prices are as of market close on the business day before the date of the report

Extra Financial-Rating

	A-	A-	C+
Environment	A-	Governance	C+
Social	A	Risk Discount	5.0%

Absolute & relative performance



Source JCF, WestLB Research, Asset4

Research analyst

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Transforming programme

Sanofi-Aventis' 'transforming' programme rests on three pillars

- increasing innovation in R&D,
- pursuing external growth opportunities and
- adapting structures to future challenges.

We believe that within this new setup, which might also lead to an increased emphasis on monoclonal antibodies, biomarker programmes could play a more important role. Within its approach of pursuing external growth opportunities we believe that Sanofi-Aventis might also consider entering the field of diagnostics, if it would serve its purpose. Thus, if more biotech-derived products enter the company's pipeline, the chances might increase that Sanofi will become involved in theranostics.

Investment case

We believe that in establishing a new management team, Sanofi-Aventis has certainly made a step towards addressing the company's underlying issues. Still it is heavily reliant on its older cardiovascular and oncology franchise, with the major growth driver being the long-acting insulin Lantus (glargine). The other growth driver is the company vaccines business – one of the few global operations in this area. Given the upcoming patent cliff as well as generic competition for Eloxation (oxalipatin) in the US, and the resulting weak EPS growth profile we remain cautious for the time being and continue to rate Sanofi-Aventis shares as Neutral.

Sanofi-Aventis divisional forecast (€m)

Year ending December	2008A	2009E	2010E	2011E	2012E	2013E	CAGR '09-'13E
Cardiovascular/Thrombosis	8,310	8,356	8,177	8,327	7,346	7,280	-2.7
% change y-o-y	1.4	0.6	-2.1	1.8	-11.8	-0.9	
Oncology	3,466	3,598	3,332	3,161	3,379	3,522	-0.4
% change y-o-y	-0.4	3.8	-7.4	-5.1	6.9	4.2	
Diabetes	3,545	4,227	4,530	4,874	5,180	5,479	5.3
% change y-o-y	11.9	19.2	7.2	7.6	6.3	5.8	
Central Nervous System	3,141	3,066	3,230	3,440	3,013	3,228	1.0
% change y-o-y	-24.0	-2.4	5.3	6.5	-12.4	7.1	
Internal Medicine	5,096	4,985	4,969	4,973	4,990	5,019	0.1
% change y-o-y	-5.9	-2.2	-0.3	0.1	0.3	0.6	
Other Rx revenues	1,149	1,092	1,037	985	936	889	-4.0
% change y-o-y	0.0	-5.0	-5.0	-5.0	-5.0	-5.0	
Total Rx revenues	24,707	25,324	25,275	25,760	24,844	25,417	0.1
% change y-o-y	-2.2	2.5	-0.2	1.9	-3.6	2.3	
Total vaccines revenues	2,861	2,982	3,253	3,555	3,891	4,183	7.0
% change y-o-y	3.0	4.2	9.1	9.3	9.5	7.5	
Total prescription/vaccine sales	28,817	29,605	29,865	30,640	29,342	30,308	0.5
% change y-o-y	-1.3	2.7	0.9	2.6	-4.2	3.3	

Source Company, WestLB Research estimates

Sanofi-Aventis profit & loss (€m)

Year ending December	2008E	2009E	2010E	2011E	2012E	2013E	CAGR '09-'13E
Group sales	28,817	29,605	29,865	30,640	29,342	30,308	0.5
% change y-o-y	-1.3	2.7	0.9	2.6	-4.2	3.3	
Cost of goods sold	-7,335	-7,531	-7,482	-7,708	-7,451	-7,732	
in % of sales	-25.5	-25.4	-25.1	-25.2	-25.4	-25.5	
Gross profit	21,482	22,074	22,383	22,932	21,891	22,576	
Gross margin (%)	74.5	74.6	74.9	74.8	74.6	74.5	
Selling, general & administrative expenses	-7,168	-7,402	-7,141	-7,320	-7,140	-7,355	
in % of sales	-26.0	-26.1	-25.0	-25.0	-24.8	-24.8	
Research & development expenses	-4,575	-4,731	-4,617	-4,740	-4,638	-4,787	
in % of sales	-15.9	-16.0	-15.5	-15.5	-15.8	-15.8	
Other operating expenses/income	344	250	250	250	250	250	
in % of sales	1.2	0.8	0.8	0.8	0.9	0.8	
Operating income/loss	9,942	10,285	10,875	11,122	10,363	10,684	0.8
Operating margin (%)	36.1	36.3	38.1	37.9	36.1	36.0	
Intangibles - amortization and impairment	-180	-179	-160	-160	-160	-160	
Financial result	-232	-254	-150	-150	-150	-150	
Exceptional items	-654	-927	0	0	0	0	
Other non-operating income/expenses	76	0	0	0	0	0	
Earnings before taxes (EBT)	8,952	8,925	10,565	10,812	10,053	10,374	
Pre-tax margin (%)	32.5	31.5	37.0	36.9	35.0	34.9	
Income taxes	-2,333	-2,890	-2,958	-3,027	-2,815	-2,905	
Tax rate (%)	-26.1	-32.4	-28.0	-28.0	-28.0	-28.0	
Equity in earnings of affiliated companies	890	1009	951	936	393	403	
Net income before minority interests	7,509	7,044	8,558	8,721	7,631	7,872	2.2
Minority interests	-441	-466	-467	-471	-444	-426	
Net income after minority interests	7,068	6,601	8,091	8,250	7,187	7,446	2.4
% change y-o-y	-0.6	-6.6	22.6	2.0	-12.9	3.6	
EPS	5.40	5.14	6.42	6.68	5.94	6.16	3.7
% change y-o-y	2.3	-4.8	25.0	4.0	-11.1	3.6	

Source Company, WestLB Research estimates

25 September 2009

Stratec Biomedical Systems

NEUTRAL

Current price €19.5

Target price n/a

Pan European Equity
Germany

Life Sciences

Medical Technology

Well positioned to benefit

Stratec could be, in an indirect way, key player in the field of theronostics and personalised medicine, through the diagnostic analyser expertise that the company offers its customers. The capabilities and product offerings of Stratec, as an OEM to eight of the top 10 *in vitro* diagnostics players, provide such companies platform solutions on which to run their tests. So with the expected explosion of molecular diagnostics and personalised medicine, we expect the demand for new analyser systems to show similar growth going forward. The recent acquisition of Invitek has expanded Stratec's product offerings and capabilities in molecular biology, and we see an increased likelihood that Stratec, by offering fast development times to its customers, will remain a partner of choice with diagnostics companies. Thus we expect the signing of new development deals to accelerate going forward.

Year end	Sales	EBT	EPS	P/E	EV/EBITDA	EV/EBIT	Yield
Dec	(€m)	(€m)	(€)	(x)	(x)	(x)	(%)
2008A	61	12	0.54	25.1	10.2	12.2	1.6
2009E	80	16	0.97	20.1	12.0	14.0	-1.8
2010E	100	20	1.26	15.4	8.9	10.1	1.5
2011E	116	24	1.47	13.2	7.3	8.3	1.9

Note: EBT figures are adjusted

Source Stratec Biomedical Systems, WestLB Research estimates

Expanding technology offerings with acquisition of Invitek

Stratec's strengths have traditionally been in providing high-throughput screening solutions to its customers, utilising its expertise in immunofluorescence assay techniques. Through partnership deals the company has designed and manufactured fully automated analyser systems for diagnostics companies such as Siemens (the ADVIA Centaur CP) to run their test menus. However, Stratec has expanded its capabilities in molecular biology with its recently announced acquisition of Initek, (nucleic acid purification and testing), thus significantly increasing opportunities to the range of services offered to its existing and potential OEM customers.

Key data

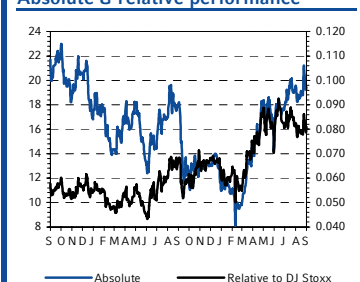
in %	1m	3m	12m
Absolute	-0.6	28.4	8.1
Relative	-1.9	10.4	19.6
12 month price range	€21.19 - €8.13		
Net cash/share YE	€1.0		
NAV/share YE	€5.3		
No. shares in issue	11.4m		
Free float	57.0%		
Market cap	€222m		
Next event	Q3 Result		
Date	19/11/2009		
Reuters code	SBSG.F		
Bloomberg code	SBS GY		
DJ Stoxx	239.98		

Unless otherwise stated, share prices are as of market close on the business day before the date of the report

Extra-Financial Rating

	n/a	Governance	n/a
Environment	n/a	Risk Discount	n/a
Social	n/a		

Absolute & relative performance



Source FactSet, WestLB Research, Asset4

Research analyst

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Collaboration with Qiagen for HPV test platform

With the identification that HPV-16 and 18 play a pivotal role in the development of cervical cancer, and the subsequent development of the vaccines Gardasil (Merck & Co) and Cervarix (GlaxoSmithKline), there is increased demand for the development of diagnostic tests to identify those patients already infected by the virus. Qiagen has developed such a test, utilising its assay technologies, but with little experience in the field of analyser systems it called upon the expertise of Stratec to develop a fully automated analyser system. The collaboration involves the design and manufacture of two systems, the JE2000 and the JE800, which marked a significant milestone for Stratec via the offering of molecular diagnostics (MDx) solution capabilities to its customers.

Collaboration with Gen-Probe over Panther

Another development agreement in the lucrative field of MDx is the partnership deal with Gen-Probe to develop the Panther analyser system to enable Gen-Probe to run its MDx tests primarily used to diagnose human diseases. The agreement was the third MDx development programme for Stratec, and highlights Stratec's commitment to this technology, considering the significant amount of reinvestment in MDx R&D.

Near-patient testing

We expect patient screening, and the need for diagnostic and predictive tests, to accelerate going forward, with ever increased understanding of theranostics and the opportunities offered by a personalised and targeted approach to future drug development. Stratec management highlights its commitment to personalised medicine and the opportunities offered by near-patient testing. We believe Stratec, with its recent experience in MDx development programmes, in addition to expanding its capabilities, is well positioned to benefit from the expected increased requirements for patient testing going forward.

Investment case

Stratec has emerged with robust sales and earnings trends as a result of the encouraging sales performance of its remaining analyser product portfolio and the strong contribution of its spare parts and maintenance kits, after a difficult 18 months owing in the main to disappointments surrounding Siemens' ADVIA Centaur CP analyser system. The company guides sales growth of between 20% and 30% for 2009 and 2010, which we believe is more than achievable with the launch of four additional analysers over the next 12 months. We believe Stratec is entering a period of sustained growth (2008-13E sales CAGR 18%), considering the company's good record of repeat business from existing customers, management comments that they are in advanced talks with new prospective customers, and the future opportunities offered through theranostics and personalised medicine.

Stratec Biomedical Systems P&L (€m)

Year ending December	2008A	2009E	2010E	2011E	2012E	2013E	CAGR 08-13E
Group sales	61	80	100	116	132	141	18.3%
<i>Change y-o-y (%)</i>	-9.7	31.0	25.2	16.2	13.4	7.1	
Overall performance	68	85	103	120	135	145	
<i>Change y-o-y (%)</i>	-2.9	25.5	21.8	15.7	13.1	7.0	
Cost of goods sold	-32	-40	-50	-57	-65	-69	
<i>% of sales</i>	52.8	-49.9	49.6	49.4	49.2	49.0	
Gross profit	35	45	54	62	70	75	16.3%
<i>% of sales</i>	52.5	53.1	52.0	52.0	52.0	52.2	
Personnel expenses	-17	-19	-23	-26	-30	-32	
<i>% of sales</i>	24.7	22.6	22.6	22.5	22.4	22.4	
Cost of services rendered	0	-1	-2	-2	-2	-2	
<i>% of sales</i>	-0.1	-1.7	1.5	1.5	1.5	1.5	
Other operating income	-5	-7	-7	-9	-10	-10	
<i>% of sales</i>	-7.8	-8.1	7.2	7.2	7.2	7.1	
Operating income (EBIT)	11	15	20	23	26	28	19.8%
<i>EBIT margin (%)</i>	18.4	18.9	19.5	19.5	19.5	19.6	
Depreciation/amortisation	-2	-3	-3	-3	-3	-4	
EBITDA	13	18	22	26	29	31	18.5%
<i>EBITDA margin (%)</i>	22.0	22.0	22.3	22.1	22.1	22.3	
Interest income/expenses	0	1	1	1	1	1	
Reported earnings before taxes (EBT)	9	16	20	24	27	29	25.3%
<i>Pre-tax margin (%)</i>	13.9	18.5	19.6	19.7	19.8	20.0	
Income taxes	-3	-5	-6	-7	-8	-8	
Net profit (after minorities)	6	11	14	17	19	21	27.4%
<i>% change y-o-y</i>	-38.6	80.5	30.1	16.7	13.1	8.2	
Reported EPS (€)	0.54	0.97	1.26	1.47	1.66	1.80	27.4%
<i>% change y-o-y</i>	-39.1	80.4	30.1	16.7	13.1	8.2	

Source Company, WestLB Research estimates

Appendix

Current theranostics

Drug company	Drug	Indication	Cost of drug	Side effects	Biomarker	Diagnostic company	Test name	Marketing status diagnostic
Oncology								
Roche (Genentech)	Herceptin	HER2+ breast cancer	\$3,000/month	Cardiac dysfunction (2-7% of cases)	HER2	Abbott Molecular	PathVysion HER-2 DNA Probe kit	FDA approved
						Dako	HercepTest	Not FDA approved
						Dako	Her2 FISH pharmDx Kit	FDA approved
						Invitrogen	SPOT-Light HER2 CISH kit	FDA approved
						Siemens Healthcare Diagnostics	Oncogene ELISA HER2	Not FDA approved
GSK	Tykerb	HER2+ breast cancer	\$3,000/month	diarrhoea, palmar-plantar erythrodysesthesia, nausea, rash, vomiting, fatigue, liver toxicity	HER2	As for Herceptin		
Roche/OSI Pharmaceuticals	Tarceva	Lung cancer	US: \$24,000/year UK: £19,600/year	Rash, diarrhoea, loss of appetite, fatigue, pnemonitis, partial hair loss	EGFR	DxS	Therascreen EGFR 29	Not FDA approved
Roche	Vesanoid (tretinoin)	AML	€418.65/100 capsules	Retinoic acid syndrome (dyspnea, fever, weight gain, peripheral oedema); teratogenicity	PML-RAR alpha	Ipsogen	Fusion Quant	Not FDA approved
	Xeloda (5FU)	Colorectal cancer, breast cancer	\$254/3 week cycle	Myocardial infarction, angina, hand-foot syndrome, diarrhoea, nausea, stomatitis, neutropenia, anaemia, thrombocytopenia, hypebilirubenia	Dihydropyrimidine dehydrogenase (DPYD) and thymidylate synthetase (TYMS)	Myriad Ventana (Roche)	Myriad's Theraguide Pathway	Not FDA approved FDA approved
Imclone (Eli Lilly), BMS, Merck KGaA/Amgen	Erbix/ Vectibix	mCRC, SCCHN mCRC	Erbix: up to €3,600/month Vectibix: c. €3,000/month	Acne-like rash	EGFR	Dako	EGFR PharmDX (no longer used as results are clinically non-significant)	Not FDA approved
					KRAS mutation	DxS/Roche	TheraScreen KRAS	Not FDA approved
						Genzyme Genetics	Genzyme's KRAS test	Not FDA approved
						Qiagen	PyroMark Q24 KRAS	Not FDA approved
						Trimgen	Mutector II	Not FDA approved
Novartis	Gleevec	Cancer/CML	\$32,000/year	Oedema, nausea, rash, musculoskeletal pain, congestive cardiac failure (rare)	BCR-abl	Cepheid	GeneXpert RUO	Not FDA approved
					c-KIT	Dako	c-KIT PharmDx IHC assay	Not FDA approved
Generic (originally AZ)	Tamoxifen	Breast cancer	US: \$40-100/month UK: £1.90/month	Prevents osteoporosis (positive!), endometrial cancer, increased risk of thromboembolism, memory impairment	ER/PR	Dako	ER/PR pharmDx	Not FDA approved
					ER	Ipsogen	MapQuant Dx	Not FDA approved
						Genzyme	EGFR mutation assay (costs \$975)	FDA approved
AZ/Teva	Iressa	Lung cancer	\$20,000/year	Rash, diarrhoea, nausea, vomiting, anorexia, stomatitis, dehydration, skin reactions, paronychia, elevations of liver enzymes, asthma, conjunctivitis, blepharitis	EGFR	DxS Genzyme	Therascreen EGFR 29 EGFR mutation assay (costs \$975)	Not FDA approved FDA approved
Yakult Honsha/ Pfizer	Camptosar (irinotecan)	Colon cancer	\$10,000/8-week regimen	Severe diarrhoea, immunosuppression	UGT1A1 (drug metabolising enzymes)	Third Wave Technologies	Invader UGT1A1 Molecular Assay	FDA approved

Source Companies, WestLB Research estimates

Current theranostics (contd.)

Infectious diseases								
Various	Anti-retroviral	HIV Quantitation HIV drug resistance testing	dependent on exact drug combination	dependent on exact drug combination	HIV	Abbott Molecular Celera Diagnostics Siemens Healthcare Diagnostics	Abbott Real-time HIV-1 (m2000) ViroSeq HIV-1 Genotyping System TruGene HIV-1 Genotyping and Open Gene DNA Sequencing System	FDA approved FDA approved FDA approved
Pfizer	Selzentry/ Celsentri	CCR5 HIV-1	\$10,585/year	upper respiratory tract infections, cough, pyrexia, rash, dizziness	CXCR4, CCR5-tropic HIV-1	Monogram	Profile assay	Not FDA approved
GSK	Abacavir (Ziagen, Trizivir, Kivexa, Epzicom)	HIV	\$3,540/year for Ziagen	hypersensitivity reaction in patients with HLA-B*5701 marker	HLA-B*5701	Olerup SSP/Qiagen	Olerup SSP® HLA-B*5701	Not FDA approved
Haematology								
BMS	Warfarin (Coumadin)	Coagulation disorders	\$9,000-12,500	Haemorrhage, osteoporosis, necrosis (rare), purple toe syndrome (rare)	CYP2C9/ VKORC1	AutoGenomics Kimball Genetics Nanosphere Osmetech Molecular Diagnostics ParagonDx	Infiniti Warfarin test Warfarin DoseAdvise Verigene Warfarin Metabolism Nucleic Acid Test eSensor Warfarin Sensitivity Test Gentris Rapid Genotyping Assay - CYP2C9 & VKORC1	Not FDA approved Not FDA approved FDA approved FDA approved FDA approved
Various								
Various	Various	Drug metabolizing Enzymes	Various	Various	Drug metabolizing Enzymes	Roche Molecular Diagnostics	AmpliChip Cytochrome P450 Genotyping Test	FDA approved

Source Companies, WestLB Research estimates

EU publicly listed theranostics companies

Country	Company	Share price at closing 24/09/2009	Currency	Market Cap (€m)	Performance ytd (%)	Theranostic-Index (weight %)	Company Description
D	EPIGENOMICS	3.05	EUR	89.65	52.50	1.06	MDx firm using DNA methylation biomarkers. One validated for the early detection of colorectal cancer in blood plasma and various in development for prostate & lung cancer detection in urine, blood and bronchial lavage specimens
	QIAGEN N.V.	14.32	EUR	3243.45	15.76	38.43	The leading global provider of sample and assay technologies; developed and markets more than 500 sample & assay products plus automated solutions. Its assay technologies include one of the broadest panels of MDx tests in the world
	STRATEC BIOMEDICAL	19.45	EUR	222.53	43.54	2.64	Designer and manufacturer of fully automated systems for its partners in the fields of clinical diagnostics & biotechnology. Its partners are mostly global players operating in the IVD industry with a strong link to MDx
B	ONCOMETHYLOME	6.05	EUR	79.62	-8.33	0.94	MDx firm developing gene methylation tests to assist physicians in effectively detecting and treating cancer as well predicting a patient's response to drug therapy & the likelihood of cancer recurrence
F	BIOMERIEUX	75.20	EUR	2966.94	25.33	35.15	World leader in the area of IVD, its offerings include instruments, reagents & software. Its products are used for providing high medical value results for cancer screening, monitoring & CV-emergencies and for diagnosing infectious diseases
	EXONHIT THERAPEUTICS	5.45	EUR	152.51	97.46	1.81	Firm is active in therapeutics & diagnostics applying its proprietary technology, based on the analysis of alternative RNA splicing, to develop innovative blood based diagnostic tests and drugs for neurodegenerative & cancer indications
	IPSOGEN	8.25	EUR	36.27	42.24	0.43	MDx firm specialized in the development, manufacturing and commercialization of diagnostic assays for breast cancer & leukemia. Also partners with life sciences firms committed to the development of 'companion diagnostic' tests
I	DIASORIN	23.15	EUR	1273.25	62.34	15.08	Active in the area of immunodiagnostics, incl. immunochemistry & infectious immunology the firm develops, manufactures & markets reagents for IVD based on various technologies incl. ELISA, CLIA & RAI
S	IDL BIOTECH	0.99	SEK	1.86	-28.78	0.02	Diagnostic company, who is developing, producing & marketing tests worldwide for the healthcare sector. Firm is active in the fields of oncology & bacteriology, and manufactures various tumor marker and a rapid Salmonella test
DK	BIOPORTO	5.90	DKK	30.37	12.38	0.36	Firm develops and markets antibodies, antibody-based products & diagnostic immunoassays for blood and urine analysis, the latter for the benefit of individual patients and to promote efficiency in the health sector
	EXIQON	13.10	DKK	53.35	-34.50	0.63	Activities incl. diagnostic tests, innovative tools for miRNA research & contract research. Firm is dedicated to personalizing the treatment for cancer patients by using its MDx tests that analyze the genetic profile of each patient's tumor
N	DIAGENIC	3.38	NOK	20.50	22.91	0.24	IVD firm developing patient-friendly tests for the early diagnosis of devastating diseases like Alzheimer & breast cancer. The patented method is based on identifying disease-specific gene signatures from blood samples
	NORDIAG	3.93	NOK	5.56	-25.85	0.07	Firm develops, manufactures and markets automated solutions (tests & instruments) for sample preparation of bacterial & human DNA. Also develops mutations tests to predict a patient's response to specific drug therapies
GB	AXIS-SHIELD	405.25	GBP	220.04	32.87	2.61	IVD firm specialises in the supply of instruments & tests for the physician's office testing market and the development, manufacture and marketing of innovative proprietary diagnostics kits (markers) in areas of clinical need incl. CV & RA
	OSMETECH	2.14	GBP	26.94	13.87	0.32	Operating in the diagnostics industry the firm is serving the MDx market targeting hospitals and reference labs. In addition to various IVD tests & platform technologies the firm markets a Warfarin Sensitivity Test
	SOURCE BIOSCIENCE	8.09	GBP	18.03	70.32	0.21	Firm provides diagnostic and screening services to the healthcare community, genetic analyses, biomolecular tools and products to academic research and the Life Sciences industry. Amongst various marker tests the firm markets is a K-RAS test
	Total			8441		100.00	
WLB EU-THERANOSTICS Universe (NO.):				16	24.63		

Source Companies, WestLB Research estimates

Changes in recommendations for issuers discussed in this report

Name	Recommendation	Previous Recommendation	Latest recommendation change date
AstraZeneca	Reduce	Neutral	25/09/2009
Bayer	Add	Neutral	29/07/2009
GlaxoSmithKline	Add	Neutral	10/11/2008
Merck KGaA	Add	Buy	26/01/2009
Novartis	Add	Neutral	25/09/2009
Qiagen	Add	Neutral	05/05/2009
Roche	Add	Neutral	25/09/2009
Sanofi-Aventis	Neutral	Add	10/11/2008
Stratec Biomedical Systems	Neutral	Buy	19/05/2009

Source WestLB Research

WestLB Equity Research: Distribution of ratings as of 24 September 2009

Coverage universe	Count	Percent	Inv. Banking Relationships*	Count	Percent
Buy/Add	66	35	Buy/Add	23	48
Neutral	82	43	Neutral	21	44
Sell/Reduce	42	22	Sell/Reduce	4	8

*Companies from which WestLB AG or an affiliate or subsidiary has received compensation for investment banking services within the past 12 months.

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