

Industry strategies on theranostics: need for structural alignment

Theranostics is said to change the way patients will manage their disease. Such a change assumes that diagnostics and therapeutics become increasingly linked based on genetic information. Companies that adhere to this vision have different strategies to address theranostics. The resulting industry dynamics are studied using findings from our own research on theranostics strategies expressed in companies' annual reports and two other major studies on pharmacogenomics. We put forward that, for structurally taking up theranostics, there is limited structural alignment between (bio)pharmaceutical companies, and specialised firms in diagnostics and pharmacogenomics. Also, regulatory authorities should take a more anticipatory stance towards diagnostic and pharmacogenomics companies.

After the completion of the human genome project in 2001, pharmacogenomics research, ie the study of the functions and interrelationships between genes and proteins in relation to drug use, steadily gained momentum. Using 'omics' technologies, such as transcriptomics, proteomics and metabonomics can also help in discovering and validating biomarkers¹. Pharmacogenomics information is used in drug R&D to stratify patient populations and in this way obtain relevant information regarding individual differences in drug response and disease susceptibility. In clinical practice this leads to (more) individualised therapy. Such practices call for a combination of therapeutics and (genetic) diagnostics. That is, diagnostic tests can become indispensable in accompanying drug development as well as daily healthcare practices due to the importance

of genetic factors. However, combining diagnostics and therapy is not a necessarily successful or new approach (blood drug levels and creatinine are monitored during aminoglycoside therapy; the same goes for insulin and blood glucose levels, and erythropoietin and Hb levels)².

Although it is sometimes regarded as being a hype, pharmacogenomics and the related combination of genetic diagnostics with therapy, which is termed 'theranostics' (also called theragnostics), has caught the attention of industry trend watchers (see **Box 1**). This is supported by emerging technological developments such as the shifting focus from single gene to multigenic disorders, in this way appending the 'classic' pharmacogenetics, and combining a diverse range of biomarkers (both genetic and proteomic). The following signs indicate the emergence of theranostics:

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1 A new series of companies arose, explicitly focusing on pharmacogenomics, among others Epigenomics AG and Interleukin Genetics (see <http://www.ilgenetics.com>)^{6,7}. It is even claimed that biotechnology companies, such as Genzyme Corporation and Genentech, are the major drivers of the targeted therapeutics growth⁸. Although (bio)pharmaceutical companies (by which we mean 'traditional' pharmaceutical companies as well as biotechnology companies with a drug pipeline) try to keep abreast by partnering with small biotech companies, or use their diagnostic divisions, eg Roche Diagnostics.

2 A consensus seems to be established that the 'one size fits all' adage will no longer apply on (bio)pharmaceutical products as it is increasingly difficult to develop 'blockbuster' drugs⁹⁻¹¹. Although (bio)pharmaceutical companies might not be eager to subdivide their patient populations for economic reasons, it can be beneficial to concentrate on niche applications ('the minibuster approach')^{12,13}. Cancer drug Gleevec/Glivec (Novartis' imatinib) is a prominent example of this approach, being first approved for small indication areas, later achieving monopolist status and expanding into other areas.

3 There is political attention due to steeply rising prices of new therapies, especially biotechnology products in oncology¹⁴, which resulted in an increasing pressure for cost-effective prescribed therapies. In addition, problems around Vioxx (Merck & Co, Inc) have increased concerns about drug safety and adverse drug reactions¹⁵. This drug caused serious side-effects such as increased risk of heart attack and stroke after it was marketed.

The 'dream' of combining therapeutics and genetic diagnostics in a revolutionary way, potentially changes two previously rather separated industries and the relations between them. In this context, Little remarked that "pharma does not exist in a vacuum – there are many other stakeholders with an interest in the development of personalised medicine"^{4,16}. After having taken a close look at the companies' strategies, our opinion is that the strategic reaction of the different types of companies is not working towards the realisation of the vision of theranostics vision¹⁷. Before we elaborate on this opinion in more depth, we will first sketch possible strategies that companies can take in enacting theranostics. In doing so, we will show that it is illuminating to study how different types of companies react to a trend like theranostics and how interactions with other kinds of companies are organised in the light of the strategies they follow.

Development strategies to embrace theranostics

As theranostics combines diagnostics and therapeutics, it brings together different industrial players into one playing field. Obviously, companies originating from the classical division between (bio)pharmaceutical products and diagnostic tests will be present. But, new and specialised companies, pharmacogenomics firms, will add to the emerging industry dynamics as well.

In reaction to the three signs and upcoming theranostics in general, these diverse range of players reconsider their position towards other firms¹⁸. In

Box I:Theranostics

Pharmacogenomics is defined as "the science and technologies associated with dividing patients or patient populations into groups on the basis of their biological response to drug treatment using a genetic test"⁶. Most studies do not solely concentrate on DNA analysis diagnostic tools, but also take into account phenotypic tests. This definition puts the emphasis on the combination of therapeutics and diagnostics. Many authors of review articles in the (bio)pharmaceutical science and industry stress this strong relationship between diagnosis, treatment, and prevention^{7,32,33,35,39}. Fierz called it the "diagnostic (Dx) – therapeutic (Rx) tandem combination"⁴⁰ and named it theranostics, although more recently also the term theragnostics is used⁴¹. The most prominent examples of pharmacogenomics diagnostics-drugs combination include:

- Herceptin (trastuzumab; Genentech/Roche and HerceptTest (Dako) or PathVysion (Vysis), acquired by Abbott Laboratories;
- Iressa (gefitinib; AstraZeneca) or Tarceva (erlotinib; Genentech/OSI Pharmaceuticals) and EGFR Mutation Assay (Genzyme Corporation).

Other examples of diagnostic tests are the Amplichip (Roche), thiopurine methyltransferase testing, and recently the Oncotype DX (Genomic Health, see: <http://www.genomichealth.com>). Other therapeutic products that are combined with tests include Erbitux (cetuximab; ImClone Systems/Bristol-Myers-Squibb/Merck & Co, Inc, Gleevec/Glivec (imatinib; Novartis). Companies that deal with pharmacogenomics have objectives ranging from bringing therapeutics to the market as well as to functioning as a service or platform company.

other words, strategic decisions whether or not to develop theranostic products, and whether the development should be done in co-operation or alone, influences the relations between industrial players. However, in emerging technological fields, like theranostics, the future directions are open-ended and far from clear, which makes companies follow different strategies. What strategies are likely and possible? We found three feasible strategies, which are described in more detail in **Box 2**.

1 First developing the therapeutic product, then the diagnostic test.

2 First developing the diagnostic test, then the therapeutic product.

3 The co-development of the diagnostic test and the therapeutic product.

Industry's reaction to theranostics

Thus far we have mentioned possible development strategies as reactions to the theranostics trend, but what is actually going on? To answer this question, we performed an extensive and systematic investigation of the strategy articulation in annual reports of 2004 addressing the issue of theranostics¹⁷. This was supplemented by a quick scan of 2005 and 2006 reports. For details on methodology see **Box 3**.

Our findings show that the various industrial players are clearly affected by the theranostics vision since they address it in their annual reports. Roughly half of the companies adhere to the possibilities that pharmacogenomics and theranostics have to offer. We further analysed to what extent the different industrial players react to the theranostics trend, and what kind of development strategies they apply. We treat these four groups of companies one at a time. Also the regulatory bodies were investigated using their publications on theranostics issues. This section concludes with two comparable studies on pharmaceutical companies' reaction to theranostics.

In terms of strategy, *(bio)pharmaceutical companies* keep focusing on the same actors (especially the regulatory bodies) as they used to do before the advent of theranostics. Although pharmacogenomics and diagnostic companies frequently mention the *(bio)pharmaceutical companies* as strategic partners in realising theranostic products in their annual reports, the *(bio)pharmaceutical companies* do not seem to need their help to pursue pharmacogenomics efforts. As a development strategy, they most often mention the tandem strategy (see **Box 2**). For those *(bio)pharmaceutical companies* that have a division dealing with diagnostics, this might work well, but the ones that do

Box 2: Theranostics strategies explained

1 First the therapeutic product, then the diagnostic test

When Iressa (gefitinib; AstraZeneca), a medicine that treats patients with advanced non-small-cell lung carcinoma (NSCLC), was on the market, it failed to prove consistent efficacy. AstraZeneca and the FDA therefore decided to pull the drug off the market. More recently, researchers discovered that patients with a positive drug reaction have a certain genetic mutation. These findings led to the development of the EGFR Mutation Assay by Genzyme Corporation. This scenario is exemplary for this strategy and is also called the 'product rescue' route^{42,43}. Another example is testing the genetically-dependent activity of drug metabolising enzymes, such as CYP450 chromosomes⁴⁴. This test from Roche Diagnostics can be applied to all drugs that are affected by the specific drug metabolising enzyme and is therefore a test that is applied to existing drugs as well. This test tends to improve drug safety, which is topical following the industry signs we mentioned.

2 First the diagnostic test, then the therapeutic product

A new diagnostic tool is developed to differentiate between patient and disease classes. Such a test will stimulate the development of specific therapeutics for the different classes⁴². This is also referred to as the 'independent' vision⁴³, because diagnostic companies develop tools independently from (bio)pharmaceutical companies. An example would be the stratification of complex diseases like cancer, schizophrenia, or Alzheimer's disease into subcategories using diagnostic tests, and the subsequent search for therapeutics in each area⁴⁵. First steps are made in disease areas such as breast cancer, in which gene expression patterns of tumours can be characterised using a genetic test (the MammaPrint test; Agendia). For the resulting subgroups tailor-made therapies can be developed.

3 Co-development of the diagnostic test and the therapeutic product – the tandem strategy

The development of diagnostics and therapies can occur in tandem, as was the case with Herceptin and HerceptTest. Genentech was developing a drug called Herceptin (trastuzumab), a monoclonal antibody that treats metastatic breast cancer. They soon discovered that the drug was far more efficacious with patients who have an over-expression of a protein receptor (HER2). In early 1998, Genentech approached Dako, a Danish diagnostics company, to develop a test to diagnose this over-expression. Regulatory approval was given, because of this matching of therapy and diagnostics⁴⁶.

not have such divisions need to somehow bridge the gap to diagnostics companies. However, their annual reports do not show an appropriate strategy like the tandem strategy.

Diagnostic companies articulate their relationship with *(bio)pharmaceutical companies* more often and more explicitly than the other way round. In these articulations, diagnostic companies position

Box 3: A study on strategy articulation on theranostics

In order to perform this research, a complete and consistent database was constructed¹⁷ in which companies listed on stock exchanges in 2004 were included. In constructing the database we drew upon other circulating lists of pharmacogenomics companies on websites (www.biospace.com and others), studies, scientific review articles and books^{6,7,47-49}, completed with searching stock listings. The industry was subdivided in different industry players that are involved in the enactment of theranostics. Five different types of industry players were distinguished of which the majority are based in the United States:

- 1 (Bio)pharmaceutical companies (generics and vaccine producers were excluded) (73 companies), eg Pfizer, GSK, and AstraZeneca.
- 2 Diagnostic divisions of (bio)pharmaceutical companies (10), eg Roche Diagnostics and Genzyme Diagnostics.
- 3 Dedicated diagnostic firms (49), eg Affymetrix and Beckman Coulter.
- 4 Dedicated pharmacogenomics companies (18), eg Epigenomics and Interleukin Genetics.
- 5 Regulatory bodies (2): the FDA and the EMEA, because of their structuring influence in the (bio)pharmaceutical industry.

Annual reports were used to elucidate the company strategies on theranostics, also focusing (if they are included) on, the often more informative, US SEC filings (such as 10-K forms). When no annual report was available, only SEC filings were used. Strategy articulation in annual reports is meaningful, since the companies' shareholders and other stakeholders will hold the company responsible for the exact text and the enactment thereupon. So, when companies express their strategy in the annual report, this implies that the issue is considered important. In the case of the regulatory bodies we used dedicated reports they issued on topics of pharmacogenomics, and co-development of therapeutics and diagnostics.

The findings presented in this article should be seen as a specific view gained from the analysis of annual reports. For example, when companies are found 'aware' of theranostics, it means they believe it is important enough to report on it. By using annual reports, we do not suggest to present the complete problem situation in the theranostics industry (as one can speak of one), but rather a specific view that complements others. These other views are based on other search strategies and methodologies, such as company alliance data, or press releases^{6,7,31}, all of which have advantages and disadvantages. Advantages of our approach include the presentation of an industry-wide scope, a focus on the content of the awareness, relationships and strategies concerning theranostics, and a relative high chance of observing reasons for not choosing a particular theranostics strategy. The latter might form a problem for all methodologies and should be taken into account when drawing conclusions: not mentioning theranostics in annual reports does not necessarily imply unawareness towards this development.

themselves as dependent on (bio)pharmaceutical companies, although some exceptions exist, such as Genomic Health with its Oncotype DX test¹⁸. Most frequently the costs of proving clinical validity through clinical trials is mentioned as a reason for seeking co-operation with (bio)pharmaceutical companies and thus follow the tandem strategy (see Box 2). Although they try to connect to the (bio)pharmaceutical companies to make such a strategy work, they mostly fail to do so, because of the 'uninvolved attitude' of (bio)pharmaceutical companies. Furthermore, in developing therapies for targeted patient groups, it is important to illustrate the safety and – more prominently – the efficacy of a diagnostic test. It even appeared to be one of the major factors in adopting decisions of diagnostic tests by physicians and healthcare professionals^{10,19}.

The diagnostic divisions of (bio)pharmaceutical companies naturally conform to their (bio)pharmaceutical parent companies when it comes to linking therapy with genetic diagnostics. The strategy they express is in line with this dependency and concerns developing diagnostic tests after the development of therapeutic products (Strategy 1). Apparently, these diagnostic divisions do not see themselves as part of the tandem strategy (Strategy 3), which is preferred by their (bio)pharmaceutical parents.

Pharmacogenomics companies are a heterogeneous set of companies because of their multilateral activities. They are not recognised as a separate set of companies by the other players in the theranostics strategy game, at least not in the annual reports. Therefore, no main strategy for this class of companies was observed. Two related studies by IPTS⁶ and Wellcome Trust⁷ emphasise this heterogeneity of activities, both identifying 12 technological development options.

Finally, *regulatory bodies* such as the FDA in the US and the EMEA in Europe, are increasingly aware of the pharmacogenomics developments and their role in them²⁰⁻²². The emphasis lies on how genomics data can be used in clinical trials in contrast to use in clinical laboratories. Following a FDA draft guideline on pharmacogenomics, (bio)pharmaceutical companies are encouraged to voluntarily submit genomics data while filing their clinical trial results for approval to the FDA^{21,23-25}. These data are then discussed in so-called 'safe harbours', ie the results of these discussions will not influence the FDA's approval decision. In this intermediary and patchwork solution, again the

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regulatory bodies concentrate on (bio)pharmaceutical companies and underexpose the role of diagnostic and pharmacogenomic companies. This can have a more formal reason, because historically and legally they focus on (bio)pharmaceutical players. In the US, the FDA does not have jurisdiction over tests that are used only within medical and clinical laboratories, the so-called 'home brew' genetic tests²⁶. Pharmacogenomics tests are mostly performed as in-house services by these clinical laboratories²⁷. They can potentially lead to new commercially viable theranostics products. However, a debate is going on at the moment whether the FDA should be able to regulate these tests as well²⁸. Moreover, also the co-development process and related regulatory approval procedures are subject to a recent consultation among various stakeholders^{23,27}, which should lead to a new version of the FDA pharmacogenomics guideline.

In Europe, the institutionalisation of regulatory bodies for theranostics has an intrinsic misfit, since diagnostics and medical devices fall outside the jurisdiction of the EMEA. Although the EMEA has organised similar protected spaces for pharmacogenomics data submissions through its Pharmacogenetics Working Party and the use of so-called 'briefing meetings', gene testing is largely regulated on the national level. This is mostly done through the use of CE-certification and good clinical practice rules. The *in vitro* diagnostics directive is an exception to this rule: the EU has attempted to harmonise this role by influencing national law²⁹. Regarding the regulation of medicines, the EMEA can approve drugs on the condition of using a genetic test, as they have done in the cases of, for example, Herceptin and Erbitux (see Box 1). This does not concern the prescription of testing *per se*, but more the approval of a drug for a certain indication, for example, Her2-overexpression in the case of Herceptin, which can only be discerned using a test³⁰.

These results are partially substantiated by comprehensive research originating from a Wellcome Trust project and an IPTS study, both of which are related because of some authors contributing to both studies. The former, performed by Webster and colleagues in 2002⁷, defined two types of companies, namely large pharmaceutical companies as well as biotechnology and genomics companies, developing pharmacogenetics. They showed an increase in alliances between these two types of companies, although these alliances were not necessarily formed for theranostics reasons. Moreover, they introduced 12 technological development

options for pharmacogenetics, of which large pharmaceutical companies are mostly focused on using pharmacogenetics for drug discovery, and improve safety and efficacy of drugs that are in development. Small pharmacogenetics firms also focused on improving safety and efficacy of licensed drugs.

The IPTS study^{6,29,31} was conducted in 2004 and is based on company profiles that were drawn using SEC filings and press releases. The 12 options were again examined and the conclusions corresponded with the Wellcome Trust study: developing products and services supporting preclinical and clinical drug development (safety and efficacy), aiding drug discovery and developing tests for prescription and disease stratification were the prominent development options. At the same time, drug rescue for efficacy and safety reasons, market extension strategies, post-marketing surveillance or the use of efficacy data in drug marketing were less popular reasons for developing pharmacogenetic tests. The IPTS study also showed that approximately 33% of the pharmacogenetics alliances concern diagnostic-related issues. Further, it appeared that 23 large pharmaceutical firms were involved in these alliances, and three large diagnostics companies account for the majority of the collaborations involving diagnostic firms. A deficiency in structural relationships between pharmaceutical and diagnostic companies was explained by the lack of commercial incentives to invest in these alliances.

To conclude, these two major studies show a larger degree of activity between pharmaceutical companies and diagnostics or pharmacogenomics companies. At the same time, the breadth of actors involved in these alliances is small.

To summarise, we presented the findings of our own research, which focused on the perspectives of four kinds of companies and regulatory bodies as it was presented in their annual reports on theranostics. These results were then compared to findings coming from two related studies.

Structural misalignment between therapeutics and diagnostics

Some industry reports, review articles and the popular media^{7,11,32-35} make the world believe that the whole industry should comply with theranostics as a novel business model for the (bio)pharmaceutical industry. However, by the large number of 'unaware' (bio)pharmaceutical companies, we do recognise that a large part of the industry will continue as they always did. We acknowledge that some stakeholders do not have the possibility or incentive to move to a co-development strategy. For example, because of client-relationships that diagnostic companies maintain with pharmaceutical

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companies, which results in the latter taking control of choosing the strategy, or the fact that diagnostic companies want to keep the involvement of regulatory bodies at bay as much as possible³⁰.

Those (bio)pharmaceutical companies that do adhere to the advent of theranostics, do not show much structural alignment with diagnostics and pharmacogenomics companies; collaborations and alliances remain *ad hoc*. At least in general, they did not mention these linkages in their annual reports, which indicates that there is no structural consideration for (bio)pharmaceutical companies to link up with diagnostics and pharmacogenomics firms. Such industry dynamics imply that (bio)pharmaceutical companies look at regulating bodies to address and work with the issue of theranostics. At the same time, diagnostic companies and the new and emerging pharmacogenomics companies are left aside by these companies and the regulating authorities. (Bio)pharmaceutical companies stay rather isolated from other companies with respect to interactions over diagnostic tools, whereas diagnostic companies try to link to these (bio)pharmaceutical companies to develop their therapy-related tests.

This strengthens our opinion that there is a gap between the observed industry dynamics and strategies that are more in line with the realisation of the emerging trend of theranostics. And although other studies (IPTS and Wellcome Trust) advance that alliances exist between these types of companies, we claim that a structural alignment is missing, ie an alignment that is durable, anticipated, and strategically inspired.

Bridging the gap

For a full-scale development and implementation of the theranostics potential, we believe that our observations indicate two directions for bridging the gap. As a first direction, (bio)pharmaceutical companies should set out a more structural, clear and anticipatory strategy on theranostics, and in this light, collaborate more closely with diagnostic and pharmacogenomic companies. In this way, theranostics becomes embedded in the overall industry dynamics, which improves the chances for success. Second, regulatory bodies should address diagnostic and pharmacogenomic companies as strategic players. By doing this, regulatory bodies can provide the right circumstances, incentives and clarity that is needed for companies to build their strategies.

In taking up these two possible solutions, there is a hurdle to overcome that concerns differences in R&D processes between (bio)pharmaceutical and diagnostic companies. One could claim that the co-development strategy is ideal for dealing with ther-

anostics. However, drug research and development is not necessarily a linear process in the sense that basic research is succeeded by clinical research and market introduction. For example, clinical research yields points of departure for basic research. More recently, in so-called 'adaptive trials', dosages and patient pools are constantly altered³⁶, and post-marketing research reveals information on safety, efficacy, disease mechanisms and unexpected indications. The well-known cases of Viagra and thalidomide are exemplary on this issue³⁷. The latter is called 'drug repositioning' and could be seen as just as important for public health as developing new drugs³⁸. This non-linear character of the drug R&D process and the fact that this process should be connected to the diagnostics R&D process makes policy and management steering more difficult. In the drug repositioning case, questions might be raised over who is responsible for rescuing drugs that seemed to be written off. Is this a market failure that legitimises the government to intervene⁷ or do companies still see a role for themselves, just as in the Amplichip case (Roche and see **Box 2**)?

Only by addressing the two aforementioned directions to bridge the gap, do industry dynamics become more in line with realising the theranostics vision. In doing so, they should take into account the complexity of R&D processes. The current *ad hoc* connections between diagnostics and therapeutics companies need to be substantiated and extended by structural, strategic linkages and alliances, which over time can generate other theranostics combinations to be realised. Moreover, regulatory authorities should include diagnostic companies in their dealing with different theranostics strategies.

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