Interview with Bernhard Sixt, President & CEO, Agendia

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Agendia has experienced remarkable growth in the seven years since you founded the company. In 2009 you expanded the company's Amsterdam facilities and, in 2010, you doubled the size of its U.S. facilities. Why this drastic expansion, especially over the last two years?

Agendia continues to grow at a rapid pace. As that happens, we continue to take steps to ensure that our laboratories have the capacity to meet growing demand for Agendia's breast cancer decision support system called Symphony. MammaPrint®, a central component of our system, is unique in that we voluntarily sought and received U.S. Food and Drug Administration (FDA) clearance. This is a significant advantage as MammaPrint is the first and only FDA cleared IVDMIA (In Vitro Diagnostic Multivariate Index Assay) on the market.

The FDA announced its plans to regulate the field and invited all companies in this space to submit their data to the agency. While this is not yet mandatory, Agendia has always taken pride in meeting the highest standards of quality and safety to ensure that we provide the best possible products to patients and physicians. To that end, we built cutting edge CLIA and CAP accredited laboratories that have FDA cleared production lines and we are compliant with ISO 17025 standards.

Agendia continues to focus on growing our presence in the U.S., where the molecular diagnostics market has been developed by first generation tests and we have the opportunity, because of our supreme clinical utility, to become an industry leader. We were proud to have MammaPrint's clinical utility validated by its inclusion in the International St. Gallen Breast Cancer Guidelines.

When laying the groundwork for our commercial operations, we took a close look at the reimbursement framework. Agendia signed its first reimbursement contract with CMS Medicare at the end of 2009, followed by a contract with Humana in 2010. Today our products are consistently covered by 28 U.S. insurance carriers.

To meet the needs of a growing company, Agendia built a world class 17,000 square foot office and laboratory facility in Irvine, California. All of these changes optimally position Agendia for continued growth and success in the U.S. and internationally. With a total of 90 people in both the U.S. and the Netherlands, Agendia is poised to be an industry leader for a long time.

What rewards does Agendia reap for all of these investments?

Once we obtained reimbursement coverage, Agendia took the next logical step; a so-called ‘proof of commercialization.’ Agendia has four products on the market for breast cancer; TargetPrint® and MammaPrint are in widespread clinical use, while BluePrint® and TheraPrint® are provided under the research use only label (RUO). These products are part of the Symphony decision support system which provides personalized information from a specific patient and helps determine the appropriate adjuvant treatment tailored to that patient. TargetPrint quantitatively measures the gene expression of ER/PR/HER2 and serves as a high quality centralized lab confirmation of receptor status. MammaPrint is a 70-gene profile which resulted from an unbiased genome-wide discovery process. It identifies tumors that have the potential to develop chemotherapy sensitive metastasis with remarkable 95 percent accuracy; BluePrint is an 80-gene profile that gives information about the functionality of the ER and Her2neu receptors. TheraPrint quantitatively measures the gene expression of 56 drug target genes.
Proof of commercialization was obtained by the 20 sales representatives we hired during 2010. With these pieces in place, the stage is set for Agendia to fully commercialize.

Over time, your competitors will also progress and expand their product line. They may even obtain FDA clearance. Does this concern you?

On the contrary. We have benefitted from competitors developing the market. Today, we have the most comprehensive decision support system in Symphony, which has supreme clinical utility. MINDACT, our clinical trial with 6,000 patients, promises a stream of new breast cancer products and will complete patient enrolment mid 2011. We are also excited that our entry into colon cancer is around the corner. We encourage our competitors to comply with FDA regulations for the sake of patient safety. We look forward to mandatory FDA regulation, which will finally ensure a level playing field. In addition, Agendia has the ability to offer so-called “pathology-on-demand,” which

allows the oncologist to instantaneously get Agendia's Symphony decision support system when he needs it, allowing decisions to be made in the first tumor board meeting. This puts Agendia in a unique position relative to our competitors. This is Agendia's Unique Selling Proposition (USP).

Why did Agendia comply with FDA clearance regulations?

It is, of course, rather unusual that our industry is not yet fully regulated with FDA oversight. There was a lot of excitement when Agendia entered the U.S. market in 2004. At that time, all players in the market were notified by the FDA that the agency intended to regulate the field. While others opposed FDA regulation of our industry, Agendia put its marketing efforts for MammaPrint on hold and cooperated with the FDA. We saw the opportunity to take the lead in creating a high standard of patient safety for our industry. This has always been fundamental to Agendia's philosophy. Our early, voluntary FDA compliance provides Agendia with a significant advantage and underpins Agendia's reputation as a leader in the industry while others still have to meet this challenge.

In 2007, Time magazine called the MammaPrint breast cancer recurrence test "cancer's crystal ball" and named it one of the five best innovations of the year. What do you feel the product brings to the patient?

While we are proud of MammaPrint, we should put this in the context of Agendia's entire breast cancer suite. The first important information for a breast cancer patient is the status of the Estrogen Receptor (ER), the Progesteron Receptor (PR) and the Her2neu Receptor (Her2neu). Routinely those receptors are measured by IHC which has known standardization issues. TargetPrint objectively and quantitatively reads the status of ER/PR/Her2neu with unrivalled quality and accuracy. The presence of the receptors provides information about the aggressiveness of the cancer and also indicates whether a cancer could potentially react to hormonal therapy or Herceptin.

The question remains; does the receptor function? BluePrint determines genes downstream of the receptors and thus measures their functionality, which is, of course, more important than its mere existence. Hormonal therapy is the most powerful breast cancer treatment, potentially saving 30 percent of breast cancer patients. Getting this decision right is not simple, as recent history shows. Relying on IHC only is not sufficient. The use of objective, high quality systems like TargetPrint and BluePrint is paramount. These two products are vital features of our Symphony decision support system.

The next question that must be answered is whether additional chemotherapy will be useful. Here, Mammaprint gives a clear answer as it stratifies patients into two groups: those with a high risk of

chemotherapy-sensitive metastasis and those with a low risk. Unfortunately, chemotherapy is not a cure and can save only a small percentage of patients, but those are almost exclusively confined to the MammaPrint high risk group. Today 85 percent of patients are being treated with chemotherapy. MammaPrint saves 35 percent of patients the burden of chemotherapy treatment and its side effects, with still an improved outcome.

This is even more important at a time when healthcare costs continue to rise and come under increased scrutiny. MammaPrint reduces the incidence of unnecessary treatment and improves the quality of treatment for those who do need it. Medical costs are reduced, patients receive better care, and many patients are spared the unnecessary burden of chemotherapy; it is truly a win-win-win situation.

Do you feel that the government is aware of the benefits Agendia provides?

Yes, I believe so. In the U.S. for example, while President Obama was still in the Senate, he and the late Senator Kennedy drafted a personalized medicine bill together. The U.S. system has come under intense pressure following the extension of healthcare coverage to millions of additional Americans. MammaPrint ensures that only those who can benefit from the therapy are treated. There is no understating the savings this creates.

Whether for commercial, clinical validation, or research reasons, you've clearly been active internationally since Agendia's inception. Are there borders to your business?

The problems associated with providing high quality, cost efficient healthcare are not unique to the U.S.; it is a worldwide issue. When MammaPrint and the other tests were made available in Europe, the level of interest in our products from clinicians, large pharma companies and governmental bodies was significant.

Along with Agendia, a group of clinicians from the Breast International Group (BIG/TRANSBIG), Roche, Novartis, Sanofi-Aventis and the European Union (6th European framework) initiated a large international trial called MINDACT. This unique 6,000 patient trial is now nearing completion. It allows us to measure the direct predictive aspects of MammaPrint to Xeloda (Roche), Taxotere (Sanofi-Aventis), Femara (Novartis), tamoxifen and Herceptin (Genentech/Roche). There is promise of new predictive markers to those drugs as Agendia uses DiscoverPrint to profile the entire genome for all of our patients. The TRANSBIG research groups and Agendia will analyze the wealth of information and can seek FDA approvals for the MINDACT data.

Agendia's MammaPrint service is also pivotal in the prestigious U.S. I-SPY 2 trial, sponsored by the Foundation for the National Institutes of Health (FNIH) and under the guidance of the FDA, with the aim of accelerating the availability of new classes of targeted breast cancer drugs. Currently PARP-, IGFR-, Angiogenesis-inhibitors from Abbott and Pfizer, and an APO/TRAIL agonist from Amgen are being tested. The trial remains open and five more drugs are under consideration. As with MINDACT, our DiscoverPrint® service will enable the discovery of specific drug response profiles. New products will be integrated seamlessly with our existing Symphony decision support system and will be available from day one to all Agendia customers.

Clearly this is an exciting time for Agendia. At the recent JPMorgan conference in California you hinted that the company could soon go public. What do you make of the attention your statement garnered?

The talk of an Agenda IPO has been overstated. What I said was that in order for Agendia to execute its full commercialization plan in the U.S., we need significant funding. I pointed out that an IPO is one way a company at this point in its development might raise funds. We have made no decision.

What new markets are you interested in as you continue to expand Agendia's reach?

While the market here is not as developed, Europe still lies close to our heart. What we experienced in Europe is that all the bigger centers, nearly 180 of them, are locked by MINDACT. Thus, it would not make sense to commercialize here heavily as long as this trial is running. When this trial comes to a close in mid 2011, obviously the European strategy will need to be reconsidered. Other regions will be considered as well. For example, in Japan we have a number of cross-validations. This and other opportunities in emerging markets will require further strategic development.

Agendia began in the Netherlands, a country renowned for its public-private partnerships (PPPs). Would you say this has been a key success factor to the company's successful trajectory in the past 7 years?

Absolutely. The Netherlands is drastically different in that sense than many other countries around the world. The Netherlands is relatively conservative in taking on new treatments, which is a benefit when it comes to tissue banks. The Netherlands Cancer Institute started a tissue bank in 1983, which now has 30,000 specimens, including a substantial number of untreated samples. This untreated population is a unique gold mine of uncontaminated knowledge. MammaPrint is a prime example of the value of this tissue bank. Because it was developed and validated in untreated

patients, it gives a clear answer to the question of whether additional chemotherapy will be effective. First generation tests, on the other hand, have been developed in a tamoxifen treated population and therefore the resulting relapse risk is only valid under the assumption that the patient will be compliant with tamoxifen for the next 5 years. Unfortunately, we know tamoxifen compliance to be around 50 percent.

Clearly there are advantages to being located here. Does this mean that the Netherlands should not worry about another Dutch company shifting out and moving entirely to the US?

Agendia has a significant base of U.S. operations in Irvine, CA. The company's research facility in the Netherlands, however, is ideally situated. For a research-orientated company, it is very important to be close to the academic world.

What are your top priorities for the near future?

We believe we have effectively moved the company into prime position by implementing a strategic risk reduction plan. We are proud that some of our industry colleagues teasingly attribute our success to a combination of German stubbornness and Dutch greed.
The next step in our journey is full blown commercialization of our breast cancer products with a focus on the U.S. market. Our extensive product line lays the foundation for our continued growth. The colon cancer segment is one area where we see great potential. Agendia is moving in this direction with ColoPrint®, our prognostic test that builds on the success and reputation of MammaPrint and our Symphony decision support system. My fellow co-founders Prof. Laura van't Veer and Prof. Rene Bernards share the vision that personalized medicine holds potential to take much of the guesswork out of cancer treatment.

Agendia's mission is to finally make personalized medicine a reality and bring the highest caliber of innovation from research bench to bedside as efficiently as possible to benefit patients now, rather than in ten years. This is what drives us and everyone who works at Agendia.

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