Dutch cancer testing lab reinforces credibility with ISO/IEC 17025:2005 accreditation

Agendia B.V., the world's first diagnostic microarray lab to obtain ISO/IEC 17025 accreditation for its breast cancer testing activities, implemented the standard from start up in 2003. Now its increased credibility as a profiling service has led to easier discussions with governmental bodies and potential partners.

by **Guido Brink**

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On 29 June 2005, Agendia B.V. was awarded accreditation to ISO/IEC 17025:1999, *General requirements for the competence of testing and calibration laboratories*, for its MammaPrint gene expression profiling service, making it the world's first gene expression microarray laboratory to be granted the distinction.

This was a significant achievement for Agendia, since the reliability and accuracy of MammaPrint is top priority. The microarray analysis is used to assess the risk of cancer recurrence in breast cancer patients, and the results can lead to major and potentially life-saving decisions.

Human tissue is removed from an Agendia sampling and shipment kit prior to microarray analysis.

Compliance to the most stringent international quality criteria for testing laboratories is essential. That is why, right from the founding of Agendia in 2003, we chose ISO/IEC 17025 criteria to guide us in setting up our new testing laboratory. And it proved to be a good choice.

A new edition of the standard, acknowledged as the international benchmark of competence of testing and calibration laboratories, has just been published, see box "About ISO/IEC 17025:2005").

'Tailor-made' cancer treatment

In the treatment of cancer, detailed information on tumour characteristics and behaviour is vital. Cancer differs in each patient. Even those diagnosed with the same type of cancer and the same stage of the disease, e.g. early stage breast cancer, can show marked differences in tumour aggressiveness, response to treatment and thus, overall clinical outcome.

Agendia offers tools and services that support **the design of 'tailor-made' treatment**

Because of these differences, "tailor-made" treatment is needed to maximise the chances of success. Agendia offers tools and services that support the design of such tailor-made treatment plans.

About ISO/IEC 17025:2005

ISO/IEC 17025:2005, *General requirements for the competence of testing and calibration laboratories** has just been published, replacing the 1999 edition. The standard is acknowledged as the international benchmark for approving the competence of the testing and calibration laboratories that play a vital role in trade, in product development and manufacturing, and in protection of the consumer.

It has been used to "accredit" (approve) some 25 000 laboratories worldwide that test products and samples, and calibrate precision instruments.

However, the influence of ISO/IEC 17025 is even greater than this figure suggests since many countries make its use a legal requirement. In addition, documents derived from it are used by laboratories in specific sectors such as medicine and microbiology.

ISO/IEC 17025:2005 contains all of the requirements that testing and calibration laboratories need to meet in order to demonstrate to customers and regulators that they operate a sound management system which puts them in full control of their processes, are technically competent, and are able to generate technically valid results. Accreditation bodies that recognize the competence of testing and calibration laboratories will use the standard as the basis for their accreditation.

The new 2005 edition results from the amendment of ISO/IEC 17025:1999 to ensure its compatibility with the requirements of ISO 9001:2000, *Quality management systems – Requirements*. This became necessary because of the generalized adoption of quality management systems conforming to ISO 9001:2000, including many of the organizations that testing and calibration laboratories serve.

Compatible

It also seeks to clarify that while compatible, the two standards are not inter-changeable. Although both standards can be used by laboratories as a framework for providing their customers with confidence that they are managing their activities, only ISO/IEC 17025 can be used to demonstrate the technical competence specific to laboratories.

Laboratories may choose to be accredited to ISO/IEC 17025, or be certified to ISO 9001:2000, or both, but the processes of accreditation and certification would still be two separate actions, although highly facilitated – both for the laboratories and the assessors – by the consistency now ensured between the two standards.

There are no essential changes to the technical requirements. The modifications relate mainly to the management requirements in the document to reflect the content of ISO 9001:2000, especially in a greater emphasis on the responsibilities of top management, on the need to demonstrate a commitment to continually improve the effectiveness of the management system, on customer satisfaction, and on internal and customer communication about the management system.

The International Laboratory Accreditation Cooperation (ILAC) has set a transition period of two years from date of publication of the new edition – 12 May 2005 – for accredited laboratories to comply with the standard's requirements.

* ISO/IEC 17025:2005, *General requirements for the competence of testing and calibration laboratories*, costs 112 Swiss francs and is available from ISO national member institutes (listed with contact details on ISO's Web site: **www.iso.org**) and from ISO Central Secretariat (**sales@iso.org**). It was developed by Working Group 25 of ISO/CASCO, Committee on conformity assessment.

A microarray is placed in a hybridization oven and incubated for at least 17 hours at a constant temperature.

Treatment risk

We developed the MammaPrint gene expression profiling service to assess the risk of metastasis (cancerous spread) and thereby cancer recurrence in breast cancer patients.

To minimize such risk, many women are administered chemotherapy and/or hormonal therapy after surgical removal of the tumour. However, retrospective studies show that many patients are over treated, i.e. they would have survived without the chemo- or hormonal therapy, while some miss follow-up therapy through misclassification.

ISO/IEC 17025
encompasses all aspects
of a testing laboratory

By focusing on the genetic characteristics of the patient's tumour, MammaPrint can accurately classify whether patients run a high risk of cancerous spread or should be considered low risk. Therefore, when used in conjunction with other clinical information, the service may provide valuable assistance for oncologists in formulating medical strategies that support more personalized oncology care. Thus the reliability and accuracy of such a classification is critical.

Wide scope

Agendia was accredited to ISO/IEC 17025 by Raad voor Accreditatie (RvA), the Dutch Accreditation Council. The first step in the implementation process was a preliminary evaluation by RvA to find out if we stood a chance of complying with the criteria, followed by a two-day formal on site audit by two RvA representatives, one focusing on general quality management, the other on the laboratory facilities and procedures.

ISO/IEC 17025 encompasses all aspects of a testing laboratory, going much further than a quality assessment of the product or procedures. The quality management part of the audit reviewed not only the actual MammaPrint analysis, but also general organizational issues such as personnel training policy, how we deal with complaints from clients and users, and calibration and maintenance of equipment.

Because of the wide scope of the issues involved, ISO/IEC 17025 procedures offer valuable insight into the overall quality activities of an organization.

The whole process
took only
one and a half years

Inside out

Our lab was turned inside out for the technical part of the audit. Every single step in the microarray procedure was scrutinised by the RvA technical expert. The audit resulted in a short nonconformities (NC's) list of nine issues to be addressed before accreditation could be granted. Because we could build on my previous experience with ISO/IEC 17025 accreditation, most elements were already compliant.

No technical NC's were observed other than requiring simple adjustment of the temperature check procedure

A patient sample is placed in a microarray analysis unit, part of Agendia's ISO/IEC 17025-accredited gene expression profiling service. Two thousand genes can be examined simultaneously in each unit.

for our hybridization ovens, and to the procedure for use of quality control samples for reference batch testing.

We solved these problems to the satisfaction of RvA within just four weeks of the audit, and ISO/IEC 17025 accreditation followed shortly after.

Fast...

The whole process from set-up of our laboratories to accreditation took only one and a half years, mainly because we could start from scratch. Because Agendia is a new company, we were able to build up all laboratory facilities and procedures with ISO/IEC 17025 criteria in mind. This was a major advantage over longer established organizations that must adapt existing facilities and convince personnel to change daily work routines.

We also benefited from previous experience of ISO/IEC 17025. Agendia is a spin-off of the Netherlands Cancer Institute. One of the company's founders, Dr. Laura van 't Veer, is head of the DNA diagnostics laboratory of the Institute's Family Cancer Clinic. As quality manager, I helped steer that laboratory through ISO/IEC 17025 accreditation for hereditary breast cancer diagnostic testing, in conjunction with several laboratory technicians now with Agendia.

...but intense

Although implementation was rapid, it was an intense process that involved much of our time and quite some cost. In addition to personnel costs, direct costs including membership of the Notified Body[1)], RvA audits and audits of suppliers by Agendia staff amounted to about 10 000 euros, and we estimate further yearly audit costs of between 4 000 to 5 000 euros to comply with ISO/IEC 17025:2005 and maintain accreditation annually.

Being accredited makes contacting and negotiating with potential partners much easier

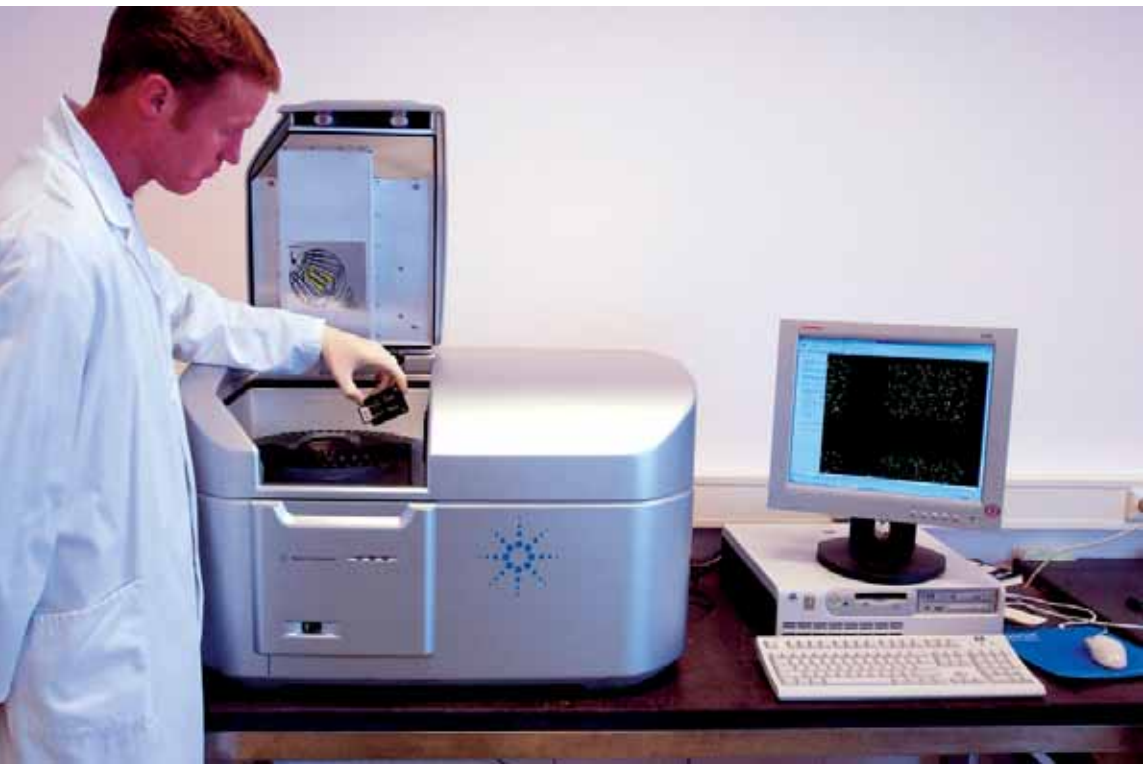
For a small start-up company, ISO/IEC 17025 accreditation is a costly process, but one that is certainly worth it. Being accredited makes contacting and negotiating with potential partners much easier. There is no need for elaborate discussions on quality matters once evidence of accreditation to the standard can be shown. We now really feel that our credibility is established, and we are taken seriously as a partner.

Furthermore, because of the wide scope of ISO/IEC 17025 requirements, we are in an excellent position to comply with other guidelines and standards, such as GLP (Good Laboratory Practice), certain FDA (US Food and Drug Administration) guidelines and European Union requirements on the construction of a CE Technical File. The whole process encouraged us to be creative and inventive, and to really think about how we want to work as a company.

Make quality your priority

Being able to start from scratch, hiring a full time quality manager with previous ISO/IEC 17025 experience and the close involvement of laboratory personnel were, in my view, the major factors in our successful accreditation process. We are convinced that making quality the top priority of your business is the key to success. •

1) Notification is an act whereby a European Commission Member State informs the Commission and the other Member States that a body, which fulfils the relevant requirements, has been designated to carry out conformity assessment according to a directive. Notification of Notified Bodies and their withdrawal are the responsibility of the notifying Member State.



A microarray scanner gives a read-out of the gene activity of a patient sample.