No. 05

CUSTOMER MAGAZINE FOR PATHOLOGY & DIAGNOSTICS

EUROPEAN EDITION

reSOLUTION

Fast and Efficient Sample Digitization

Virtual Microscopy Optimizes Histological Examinations

What Really Matters!

Leica BOND III is Part of Total Histology Solutions

Delivering Diagnostic Confidence in HER2 IHC Testing

Bond™ Oracle™ HER2 IHC System

EDITORIAL

Dear Readers,

What really matters in your profession? Better patient care – and that's the central theme of all the features in this issue of reSolution for Pathology and Diagnostics and also of Leica's Total Histology Solutions.

Total Histology Solutions combines all the elements of tissue-based pathology so that instruments and consumables form complete systems and one partner can support your entire workflow.

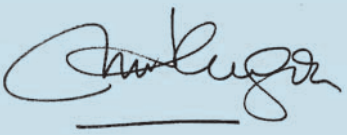
The importance of the perfect interplay of antibodies and stainers in the workflow is shown by the two interviews with customers from large hospitals: Two lab managers report on their practical experience of ready-to-use reagents. To tie in with this, we include a case study on the subject of theranostics describing the implementation of a fully automated IHC system.

This issue also contains first-hand experience in microtomy: A renowned expert tells you how to find the right knife angle and thus perfect your tissue sectioning technique.

You can only provide better patient care if you can do your work in an ergonomically comfortable position. For this reason, we have taken a close look at ergonomics and interviewed a physiotherapist on the subject. Benefit from his valuable tips.

Have fun reading!

Anja Schué
Communications & Corporate Identity



Marie-Noëlle Hugon
Marketing Manager Clinical Europe

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Virtual Microscopy Optimizes Histological Examinations

Fast and Efficient Sample Digitization

Blagovesta Wegner, Leica Microsystems

With its unprecedented scanning speed and top-quality on-screen imaging, the new Leica SCN400 Slide Scanner offers an alternative to the microscope for the examination of histological samples in pathology, research, and teaching. The Leica custom tailored lens for a digital sensor, specially designed for high-res scans, ensures that the resolution and color fidelity of the image on the screen are just as good as that of the microscope image. Thanks to the Dynamic Focus principle which keeps the sample in focus for the full duration of the scan, even difficult samples can be effortlessly digitized with the Leica SCN400. Individual settings such as choice of color or contrast are made on the finished scan to suit the user.

Highlights:

- Ultra fast scanning rate for high resolution scanning
- Leica custom lens perfected for digital imaging
- Dynamic focus mechanism for ensuring scanning even with difficult samples
- Digitization of thick samples by multi-layer scanning
- Parallel on-screen viewing of different specimens
- Worldwide remote diagnosis through protected data access
- Easy and flexible online access to digital images through Digital Image Hub
- Easy connectivity with third party software

For everyday diagnosis: speed and efficiency

The Leica SCN400 is able to load and scan up to four specimens at a time. With a scanning rate of 100 seconds per 15 x 15 mm at 20x magnification, sample throughput is substantially increased. Equipped with a powerful software, the image and data export from acquire and/or review workflow steps is very fast. The Leica SL801 autoloading system is capable of scanning up to 384 samples at the same time, overnight if required, offering completely new options for automated operation. The user can keep loading new samples or remove finished scans without interrupting the process. In hospitals, scanned images can be used in the patient's records. Thanks to digitization, there are no more problems with transportation or loss of samples.

Quality control, documentation and storage

The Leica SCN400 provides a quick and inexpensive way of sending digitized samples to associates and colleagues all over the world for mutual discussion, enabling users to obtain second opinions and meet the growing quality requirements in medical diagnosis.

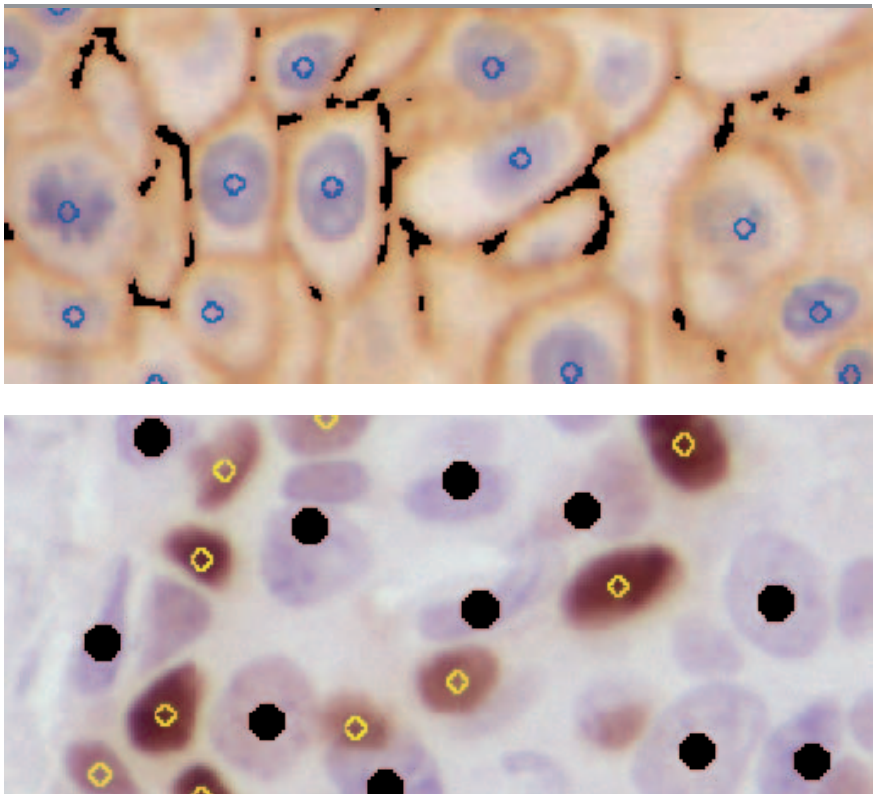


Fig. 1: Nuclear (ER & PR), Membrane (Her2/neu) capture and analysis

Fig. 2: The Leica SCN400 makes it easy to discuss digitized samples with colleagues and associates all over the world.

Besides saving time and money sending the valuable samples, the risk of broken slides is also eliminated.

Efficient image management

The Digital Image Hub from Slide Path, which has been integrated with the Leica SCN400, makes online access to digital images easy and flexible. User defined image-associated data facilitate intuitive archiving, search and retrieval. A centralized multi-format image library includes digital slides, DICOM and standard image formats. The flexible storage architecture ensures system scalability and future proofing. The software Leica SCN400 client facilitates easy connectivity with third party software.

Optimal evaluation and analysis results

Numerous evaluation and analysis functions lead to optimal research results: The Leica SCN400 can even scan thick samples in up to one hundred z layers. Length and area measurements can be taken of the digitized specimens, and tissue microarrays (TMA) can be reviewed on screen. All the data is available at any time and any place for specialist discussions among colleagues through secure database with login.

Flexibility with Ariol® platform

The Ariol® platform from Genetix, a company recently acquired by Leica Microsystems, provides the user with unmatched flexibility and high quality in microscope-based slide scanning. It offers multiple magnification options from low power to oil immersion, up to 100x objectives. Optional analysis capabilities improve the diagnostic image quality. For specific requirements the objectives, camera and filters can be customized.

New avenues for interactive teaching

The Leica SCN400 opens up new avenues for interactive teaching. Able to see the scanned specimen at the same time on one or more monitors, students can watch a sample being examined in real time. Interesting, rare or classic case studies can be easily and safely stored together with annotations for teaching purposes and retrieved by students via the Internet as needed. There's no more need to fiddle with specimen slides, and valuable samples are well protected from damage. Using Slide Path's Digital Slide Box, class size can be increased while saving costs.

Advanced image analysis tools for improved and reproducible results

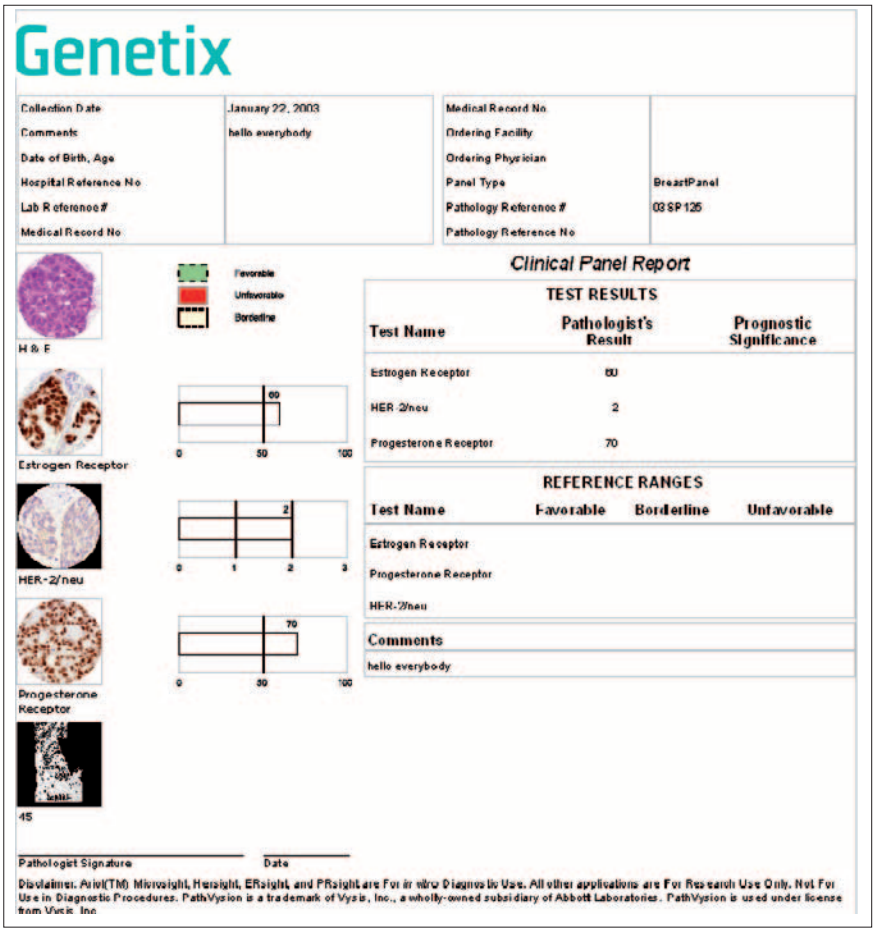
With the integration of Slide Path's Tissue IA and the Ariol® platform there are two quantitative imaging analysis tools which enable the identification and stratification of cohorts, accelerating experimental analysis and improving results.

Slide Path's Tissue IA provides high-throughput web enabled analysis for digital slides.

- Web-deployed software enables control and review of image analysis from anywhere
- Flexible solution for whole slide, region of interest or TMA analysis
- Standard algorithms (membrane, nuclear and positive pixel) can be adapted for multiple biomarker and tissue typed
- Grid computing approach enables whole slide analysis in minutes
- Scalable solution to increase processing power and decrease analysis time

The **Ariol® platform** couples high quality imaging with advanced intelligent analysis for Clinical HER2/neu brightfield IHC, ER, PR and breast cancer analysis

- Gold Standard scoring protocols fully supported (Allred scoring, Histoscoring)
- Unique region-of-interest analysis readily integrates into existing pathology workflows
- Produce case reports with easy export into information management systems


Genetix

Collection Date: January 22, 2003
Comments: hello everybody
Date of Birth, Age:
Hospital Reference No:
Lab Reference #:
Medical Record No:
Medical Record No:
Ordering Facility:
Ordering Physician:
Panel Type: BreastPanel
Pathology Reference #: 03 SP 125
Pathology Reference No:

Clinical Panel Report

TEST RESULTS

Test Name	Pathologist's Result	Prognostic Significance
Estrogen Receptor	80	
HER-2/neu	2	
Progesterone Receptor	70	

REFERENCE RANGES

Test Name	Favorable	Borderline	Unfavorable
Estrogen Receptor			
Progesterone Receptor			
HER-2/neu			

Comments: hello everybody

H & E
Estrogen Receptor
HER-2/neu
Progesterone Receptor
45

Favorable
Unfavorable
Borderline

Pathologist Signature
Date

Disclaimer: Ariol(TM) Microsight, Hersight, ERsight, and PRsight are For in vitro Diagnostic Use. All other applications are For Research Use Only. Not For Use in Diagnostic Procedures. PathVysion is a trademark of Vysis, Inc., a wholly-owned subsidiary of Abbott Laboratories. PathVysion is used under license from Vysis, Inc.

Fig. 3: Case reports can easily be exported into information management systems.

Strengthening Portfolio for Pathology & Diagnostics

Genetix Ltd, a leading provider of solutions for imaging and image analysis, has recently been acquired by Leica Microsystems. This acquisition brings together Genetix' expertise in developing and marketing imaging systems and software for research and clinical applications, with Leica Microsystems' microscopes and other life science instrumentation. The merger will enable both companies to fully realize their potential through the combination of their ideally complemented skill sets.

Stefan Traeger, Managing Director Life Science Division, Leica Microsystems, emphasizes: "Genetix' software capabilities, specifically in analytical software, will help us to make progress in the area of virtual microscopy. In addition, Genetix' experience and market leading products in cell biology and genetics will expand our reach into the drug discovery and development markets." Genetix most important products are the Ariol® platform for the quantification of tissue biomarkers, the CytoVision® platform as a multi-application solution for bright-field and fluorescence applications, and the CellReporter™ system for the quantification of cellular responses.

Leica BOND III is Part of Total Histology Solutions

What Really Matters!

Leica BOND III, the fully automated IHC and ISH stainer, is part of Leica Microsystems' Total Histology that brings together products, quality and support. Thanks to its speed, Leica BOND III enables any laboratory to achieve greater efficiency in workflow, enhanced diagnostic clarity and better patient care. Optimized reagent-use minimizes maintenance and waste disposal costs. A full range of ready-to-use antibodies specially developed for Leica BOND III ensures consistently high-quality staining for reliable accurate diagnosis.

Speed

Three additional robots for bulk fluid dispensing enable shorter turnaround times, thereby providing stained slides to pathologists more quickly. Three independent trays of 10 slides each allow continuous parallel processing of your workload. The onboard reagent capacity of 36 reagents in four trays provides the flexibility to perform IHC and ISH simultaneously.

Efficiency

Leica BOND III uses less reagents and produces less hazardous waste than any other fully automated system. Thus, it needs less maintenance, cuts waste disposal costs and reduces environmental impact. High-capacity containers require less reagent and waste management, and can be filled without removal from the instrument. Combined with the real-time fluid status all allows for more efficient reagent management. Designed to optimize Lean Histology workflows, Leica BOND III increases uptime and reduces waste, while also providing LIS connectivity, eliminating the need for double data entry.

Quality

Leica Microsystems' patented Covertile ensures preseved tissue integrity with low reagent volume, offering uniform reagent coverage throughout the staining process, cost savings and minimizing repeats. A full range of Bond ready-to-use antibodies, designed with Novocastra Science™ is preoptimized for BOND III to ensure consistently high-quality staining. High concentration of enzyme for each antibody assures stains are crisp and well-defined, providing highly sensitive detection and specificity without background staining.

With speed, efficiency and quality, Leica BOND III helps laboratories deliver what really matters: better patient care.

Leica BOND III helps to deliver better patient care through

speed,

efficiency,

and quality.

Bond RTU Antibodies: Load – Select – Run – Review

118 Ways to Improve IHC Staining

James Anderson, Leica Microsystems

Immunohistochemistry (IHC) is an essential tool for cancer diagnosis and as such standardization of testing techniques is critical. Ready-to-use antibodies on an automated platform can provide laboratories with a more reliable, reproducible method for IHC, helping to improve the accuracy of results. Leica Microsystems continues to provide laboratories with high-quality IHC with the release of eight important new antibodies in the Bond ready-to-use (RTU) format.

Renowned for being the easiest way to consistently produce diagnostic-quality IHC slides, the Bond RTU format replaces dilution, titration and mixing with a simple 4-step process:

1. Load – place a registered container on Leica BOND
2. Select – the antibody and the optimized protocol is automatically selected
3. Run – just press start and walk away
4. Review – the consistently high quality results

Now laboratories can improve efficiency and reduce human error with these new Leica Bond RTU antibodies:

- Beta-Catenin (clone 17C2)
- Cytokeratin 17 (clone E3)
- Gastrin (polyclonal)
- Galectin-3 (clone 9C4)
- Ki67 (clone K2)
- MLH1 (Mismatch Repair Protein) (clone ES05)
- Multiple Myeloma Oncogene 1 (MUM1) (clone EAU32)
- Tartrate-Resistance Acid Phosphatase (clone 26E5)

Clinical relevance

Each new product has been selected for superior performance and clinical relevance. A highlight of this release is the new K2 clone for Ki67. This new clone has shown exceptional results during development and is now recommended as the preferred Ki67 clone for the assessment of cell proliferation in normal and neoplastic tissues (although the older MM1 clone will also continue to be available). Another antibody sure to be of great interest is MLH1, which assists in identifying individuals predisposed for hereditary non-polyposis colorectal cancer. Tartrate-Resistance Acid Phosphatase – often used in panels for identifying hairy cell leukemia – and Multiple Myeloma Oncogene 1 (MUM1) – useful in panels for the identification or characterization of B cell and Hodgkin's lymphoma – are other new products that will quickly find clinical use.

Proven performers

The exceptional performance expected of a Bond RTU is maintained in these new mouse monoclonal and polyclonal antibodies. Each is a proven performer developed from existing Novocastra™ clones extensively tested in formalin-fixed, paraffin-embedded tissue. All antibodies are CE, IVD marked and are suitable for clinical use.

These new products expand the range of Bond ready-to-use antibodies to 118 antibodies worldwide (117 in the USA). All these antibodies are now available from Leica Microsystems or the authorized BOND system distributor in each region.

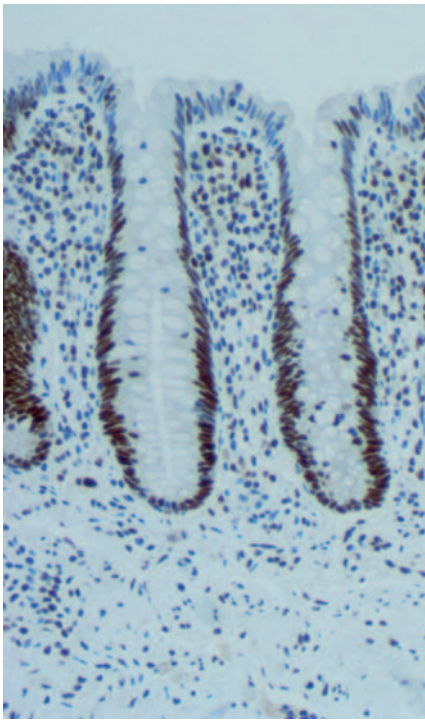


Fig. 1: Appendix stained with MLH1 (ES05)

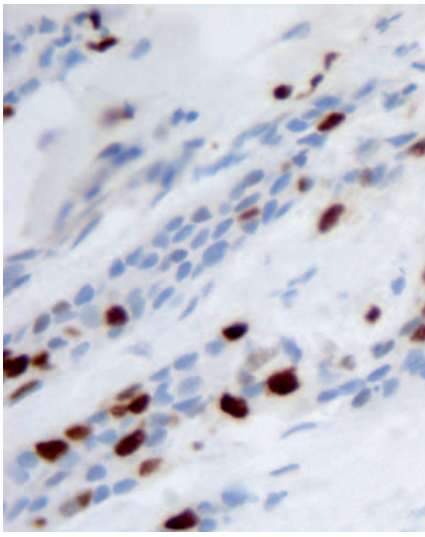


Fig. 2: Invasive Ductal Carcinoma stained with Ki67 PA0230

118 Ways to Improve IHC Staining

"Quality and Reliability – Time Saving

Helen Kidd, Leica Microsystems

Ready-to-use antibodies improve workflow and save time in a routine diagnostic laboratory. Does the same thing follow for a busy reference laboratory? Philippa Jones, Clinical Services Manager at UCL-Advanced Diagnostics, London discusses the impact of using Bond ready-to-use (RTU) antibodies in her laboratory.

Ms. Jones, how many IHC slides do you test each year?

This year we are looking at in excess of 80,000 slides. Work from our hospital comprises approximately 40% of these slides and the remainder are cases referred to us from labs all over the UK.

How do you feel that the Bond RTU antibodies cope with the wide range of tissue that you see?

For the RTU antibodies that we use they work fine. As with the concentrated antibodies that we get from Leica Microsystems, we don't change the concentration, only the retrieval if necessary. We actually do this in less than 1% of slides that we stain overall as the RTU antibodies are optimized to work with the majority of processed tissue.

How do you rate the quality of staining for the Bond RTU antibodies currently in use in your laboratory?

Excellent, otherwise we wouldn't use them! When changing from existing antibodies for any reason we will only use a new one if it is at least as good as the one it is replacing.

Do ready-to-use Antibodies Make an

Jimmy Conheady, the Chief Medical Scientist at Connolly Hospital Blanchardstown, Dublin, Ireland describes the impact that ready-to-use (RTU) antibodies have made in his laboratory.

How many antibodies do you have in your current antibody panel and what proportion of those are Bond™ RTU primary antibodies?

We have 67 antibodies in the panel and 32 of these are RTU antibodies.

What made you decide to switch to using Bond RTU primary antibodies?

We looked at RTUs because of staff shortages and difficulties recruiting new staff. RTUs have the advantages of ease of use, quality and price.

Why do you prefer using RTU antibodies to antibody concentrates?

There is no definitive way of knowing the stability of an antibody once it has been diluted. Control tissue may not pick up on subtle changes in antibody deterioration once diluted. RTUs take away this worry and provide better standardization, and an expiry date from the manufacturer guarantees shelf life. Also, potential errors from dilutions are eliminated and stock control is easier so a wider panel of antibodies can be stocked in a more cost efficient manner. It is easier to troubleshoot problems with RTUs, which is important as about 65% of lab cost is labor and RTUs free up time for staff to take on other tasks.

and Easy to Use”

Some labs consider having a set concentration of antibody as in the ready-to-use format is a less skilful option for their staff. What are your thoughts on this?

I have to admit that I was wary to start with, but having tried lots of the Bond RTU antibodies I am now converted. You haven't lost control and if necessary the epitope retrieval can be adjusted. These are routine antibodies and don't require a lot of manipulation. For a person like me, who likes to be in control, it was most unexpected that I have accepted the Bond RTU antibodies so easily and been prepared to relinquish that part of the IHC process.

What is it about using the Bond RTU antibodies that appeals to you?

Quality, reliability, time saving and easy to use – you just scan it and load it on! RTU antibodies give reproducible results and are quicker to use as there are less things to do before pressing “start” on Bond.

As a lab manager, I like the fact that stock control is much simpler. At present we aim to have a minimum of two RTU antibodies available, when one is in stock and one in use we order a new one. This is especially useful for the antibodies that we don't use so often as like other labs we cannot afford to keep stocks of concentrates that may go out of date before we have used them.

How many antibodies do you have at present in your repertoire?

We carry more than 200 antibodies of which over 70 Bond RTU antibodies are either in routine use or will be just as soon as we have used up our existing stocks of concentrated antibody.

Philippa Jones, Clinical Services Manager at University College London, Advanced Diagnostics.

Impact in the Laboratory?

What difference has the use of RTU antibodies made to your workflow and productivity?

The ease of use increases the efficiency of the Bond system. The quality is generally very good and we can stock rarely used antibodies confidently and in a more cost effective manner. The fact that antibodies do not have to be made up every day increases the speed in which the tests can be performed. Additionally, the use of Bond RTU antibodies has saved us between a half and one hour every day and we have approximately 90 % less repeat testing.

What about staining quality and antibody range?

Bond RTU primary antibodies have definitely increased the reproducibility of results and improved our lab´s performance in quality assurance testing.

Overall, how would you rate the range and staining quality of Bond RTU primary antibodies?

Excellent, no complaints with the Bond RTU antibodies in our routine panel.

Registering a Bond reagent

Chief Medical Scientist Jimmy Conheady of the Connolly Hospital Blanchardstown in Dublin.

Bond™ Oracle™ HER2 IHC System

Diagnostic Confidence in HER2 IHC Testing

Louise Flintoft, Leica Microsystems

Theranostics is understood as the growing alliance between diagnostics and therapy. A therapeutic drug is linked to a specific diagnostic test that helps select patients who could benefit from this drug. In the field of theranostics, industrial partners like Leica Microsystems can make significant contributions to the quality and reliability of prognostic and predictive assays.

HER2 Immunohistochemistry (IHC) is among the most well known of theranostic tests. HER2 oncoprotein is over-expressed in up to 30% of invasive breast cancer cases [1, 2, 3] and therefore accurately assessing HER2 status is essential for identifying breast cancer patients who might benefit from HER2-targeted therapies such as Herceptin®.

Highest reagent quality and testing consistency

Most breast cancer cases are screened for HER2 status initially by using IHC to assess the protein expression on the membrane. Equivocal cases are reflexed for more expensive in situ hybridization (ISH) techniques, which enumerate the gene copy number. HER2 testing using IHC targets the HER2 protein located on the cell membrane. HER2 IHC utilizes a target-specific primary antibody to label the HER2 protein. This antibody is then visualized using a multi step detection process.

"We decided to employ a system that from a technical perspective was completely automated, cost-effective, easy to interpret and consistently passed UKNEQAS assessments. After a period of validation it was obvious that the Oracle system would meet our requirements. We are confident we are providing an excellent service to our clinicians and ultimately to our patients."
Anthony Gledhill, Salford Royal Hospital, UK.

The sample is then viewed under bright field microscopy and the expression level is semi-quantitatively assessed using a scoring criterion that takes into account both the percentage of cell staining and the intensity of the staining. By virtue of its semi-quantitative nature, HER2 testing by IHC demands the highest level of reagent quality and testing consistency.

Fully automated IHC process

Consistency and reproducibility in the Bond™ Oracle™ HER2 IHC system is assured by automating all of the steps from dewax to counterstain and through the use of internal cell line controls. Control cell lines can be used to validate reagent optimization and performance, correct protocol implementation and instrumentation performance. Variations in section thickness have been shown to affect the reported HER2 profile[4].

It is clear that this also applies to control cell lines, which must therefore be manufactured to be as consistent as possible. Oracle HER2 Control Slides provide a comprehensive control method for assessing consistency of assay performance utilizing a system of four cell lines.

The addition of a 2+ cell line provides additional confidence, by more closely monitoring the potential for assay variation. Each Oracle HER2 Control Slide is non-destructively QC tested using a patented white light interferometry system[4]. This unique process means accurate section thickness is maintained and control slides stain consistently. This level of control is critical to achieving accurate HER2 assay validation and continuous batch performance.

Improving patient care

The Bond™ Oracle™ HER2 IHC System creates consistent quality and high-productivity workflows by automating the entire staining process. Full automation eliminates the areas where inconsistencies can be introduced, by standardizing epitope retrieval temperature and time and timing of protocol steps whilst freeing staff for other duties.

The Bond™ Oracle™ HER2 IHC System ready to-use reagents mean that inconsistencies due to errors in dilution and batch variation are eliminated.

Together these features can improve turn-around-time and reduce repeats. As the Leica BOND stainer is doing most of the work there is no need to batch HER2 slides. The average time from request to report is reduced, ultimately improving patient care.

Interactive course

For more information on the Bond™ Oracle™ HER2 IHC system check out our e-learning module:

www.leica-microsystems.com/TA9145-elearning/

The interactive e-learning course assists histologists and pathologists considering HER2 testing by covering all aspects of the Bond™ Oracle™ HER2 IHC system staining and interpretation. The inclusion of engaging, interactive exercises and tests encourage students and help check progress.

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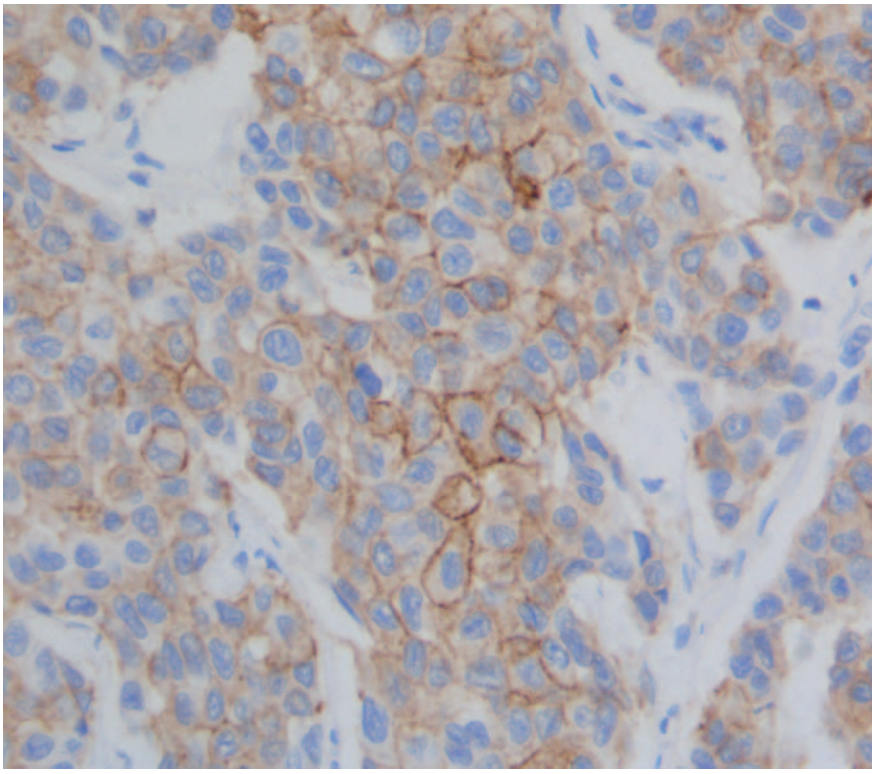


Fig.1: Invasive breast carcinoma stained with the Bond™ Oracle™ HER2 IHC System - 2+ expression

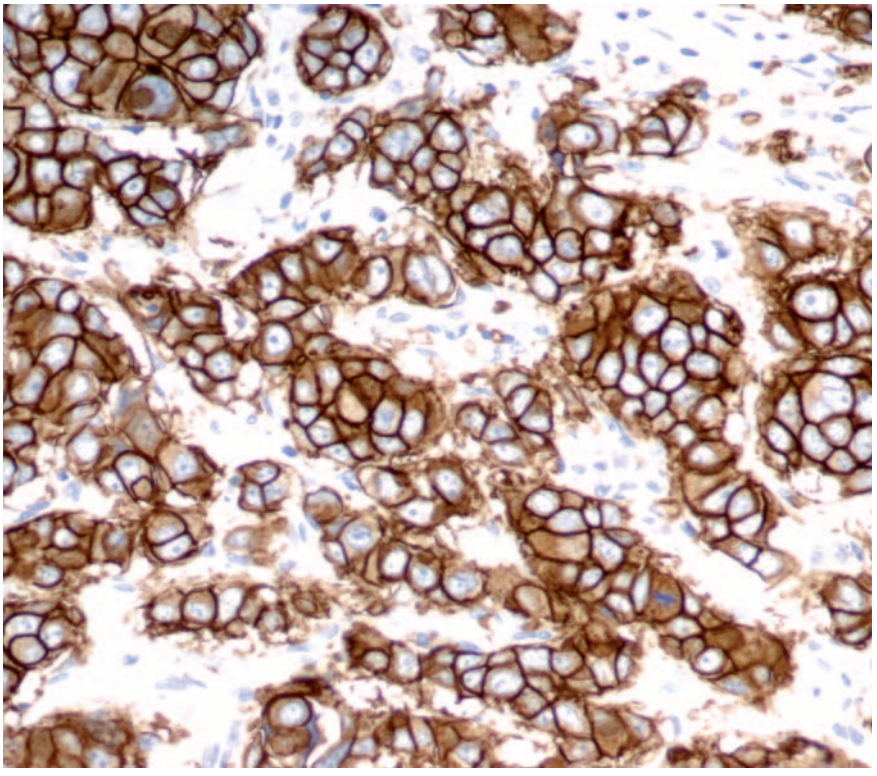


Fig. 2: Invasive breast carcinoma stained with the Bond™ Oracle™ HER2 IHC System - 3+ expression

A Biomedical Scientist Reports on His Experiences

Oracle HER2 IHC – a BMS Perspective

Anthony Gledhill, Salford Royal Hospital, UK

Testing for HER2 oncoprotein expression is commonly performed using immunohistochemistry (IHC) techniques, to determine which breast cancer patients will or will not respond to treatment with Herceptin®. Many commonly used methods are semi-automated, and introduction of manual steps can lead to high levels of variability and, consequently, unnecessary confirmatory testing by fluorescence in situ hybridization (FISH). At Salford Royal Hospital in Manchester, UK the team of the Cellular Pathology Laboratory has discussed the implementation of a fully automated test kit which has gained valuable time for the staff and given the laboratory a more reliable and consistent screening method.

Fig. 1: Anthony Gledhill, BMS3 in Cellular Pathology at Salford Royal Hospital, Manchester, UK, and his team are highly pleased with the fully automated solution from Leica Microsystems.

In October 2005, the Department of Health in the UK announced that all newly diagnosed breast cancers would be tested for the HER2 (human epidermal growth factor receptor 2) oncoprotein to assess their suitability for treatment with Herceptin. Immunohistochemistry techniques offer a relatively inexpensive, semi-quantitative assay for the pre-screening of tumor samples, with manual fluorescence or chromagenic in situ hybridization techniques (FISH, CISH) used to provide definitive testing for over-expression of HER2, albeit at a higher cost.

Unsatisfying semi-automated methods

Soon after the 2005 announcement, the Cellular Pathology Laboratory at Salford Royal Hospital tendered for, and was awarded, the HER2 testing service for a third of the Manchester and Cheshire hospital network. At this time, the department relied on a semi-automated method using a standardized kit (Dako HercepTest™) which, despite regularly passing NEQAS evaluations, was not ideal, as it required two staff members experienced in IHC to deliver the service. The semi-automated nature of testing took up an unacceptable amount of the scientists' time, due to the manual retrieval of the slides and the overall care and precision required to achieve consistent results, and it was still subject to sporadic variability, with some batches having up to 40 % of tumour samples giving equivocal results and requiring confirmation with FISH (Abbott PathVysion®). Common issues included excessive cytoplasmic staining and edge artefacts, and there were sometimes inexplicable incidents where, for example, some slides within a batch appeared to be over-retrieved but others were not. Despite strictly following the SOP, batches still varied significantly, often for no apparent reason.

Based on previous staff experience with a fully automated advanced staining platform – the BOND system from Leica Microsystems – the Salford team looked at using this platform in conjunction with a comprehensive HER2 test kit (Leica Bond™ Oracle™ HER2 IHC System). This kit employs ready-to-use reagents and affinity purified CB11 antibody to ensure consistent quality and dilution, and integrated cell lines to offer a consistent approach to assay validation.

The fully automated approach provides high levels of repeatability and can process up to twelve patient samples at a time, in three independent slide trays, including HER2 positive and negative controls for each sample, and in-house tissue and cell line assay validation controls for each run. The improvement in consistency compared to the previous method was immediately apparent, and a full validation of prospective and retrospective patient cases followed. Validation of a cohort of 100 cases took six weeks, with an emphasis on 2+ cases, as this is the equivocal range where a change in the score can affect patient treatment. Although both assays were able to successfully identify positive (3+) and negative (0-1+) cases, many cases that had previously identified as 2+ HercepTest/FISH negative stained 0-1+ with the Oracle assay, reducing the workload for FISH analysis. In a further study of 26 retrospective cases, all samples that were 2+ HercepTest/FISH amplified stained 2 – 3+ using the Oracle kit.

Leica solutions provide convincing results

Overall, the results of the new test were significantly better with regard to both consistency and correlation with FISH. Departmental histopathologists were satisfied that the cell lines were staining as expected, and of those cases previously scored equivocal 2+ HercepTest/FISH amplified, a majority came out as 3+ or strong 2+. Conversely, many of those previously identified as 2+ HercepTest/FISH negative scored 1+ or negative with the new system (see Table 1).

On the strength of this validation data, and an overall positive experience, the laboratory was able to apply for funds for a Leica BOND-MAX instrument, which was implemented for all routine HER2 testing in January 2009. This system proved so successful that an additional instrument was procured later in the same year, enabling additional IHC testing to be performed.

On average, only 23 % of cases now require confirmation by FISH*, offering significant time savings and halving the cost per test for HER2 diagnosis. Full walkaway automation releases staff for other tasks, and time is also saved by eliminating periodic re-optimization and revalidation procedures. Running the HER2 IHC assay is no longer restricted to specific scientists in the laboratory, and staff have greater confidence in results, leading to fewer repeat tests.

The Leica BOND-MAX instruments easily cope with the laboratory's HER2 screening, plus 60 % of the laboratory's additional IHC workload, and turnaround of results, which used to be up to two weeks, has been cut to just one or two days. This increase in capacity and efficiency, particularly in HER2 testing, means that the Salford department has been able to expand its cellular pathology services, absorbing additional workload from the surrounding regions.

* Based on data from January to June 2010

		Leica Bond Oracle HER2 IHC System		
		Negative	2+	3+
Dako HercepTest	Negative	32	2	-
	2+	21	2	2
	3+	-	8	7

Table 1: Prospective testing data comparing HercepTest and Oracle IHC assays

Fig. 2: The Bond™ Oracle™ HER2 IHC System includes all the reagents needed to perform up to 60 optimized immunohistochemical assays for the detection of HER2 oncoprotein when coupled with standard Bond ancillary reagents.

Fig. 3: The Bond™ Oracle™ HER2 IHC System offers a fully automated, robust and dependable test for the accurate assessment of HER2 status in breast tissue.

Lean Laboratory Design

Setting up a State of the Art Laboratory

Dr. Katja Lehmann, Leica Microsystems

No matter which opportunity you are pursuing: Building a new laboratory or re-designing an existing facility, you will be faced with plenty of challenges but also with the opportunity to execute it in a LEAN fashion, according to workflow.

The latter will have an impact on your laboratory´s performance in terms of: faster turnaround time, cost reduction and safer work environment.

Faster turnaround time:

- eliminating multiple data entry points, paper trails
- reducing the number of hand offs and decreasing cycle time

Cost reduction:

- through a smarter Inventory Management System (Kanban, FIFO) to manage replenishment cycles and reduce disposal of expired consumables
- decreased consumable costs through Reagent Management Systems
- eliminating cost of buying and disposing of hazardous waste (xylene free) and the use of consumables appropriate for the procedure and instrument (e.g. biopsy cassettes to eliminate the carry over from sponges, ActivFlo cassettes for better fluid exchange)

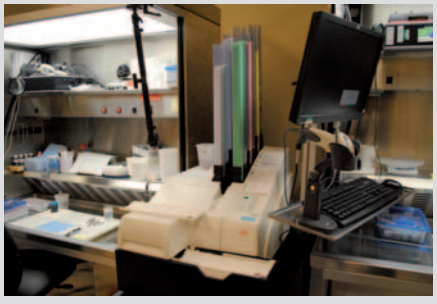
Safer work environment:

- decreasing repetitive motion steps
- less exposure to hazardous chemicals (xylene-free work)
- less stressful work environment will reduce errors and accidents

As with every large-scale project the pre-planning stage is very crucial and in addition to basic decisions about the budget, the architect and the facility, you need to have clarity about the specimen volume and types you will process, the amount and type of equipment to be installed in the laboratory and the number of employees and shifts in order to design or re-design the laboratory in a LEAN fashion.

Regardless of whether you do have an existing blueprint or start with a clean slate, your first step should be drawing a high level process map (Value Stream Map) to identify the process and information flow for all laboratory areas (AP, IHC, Cytology, etc.) This will visualize the basic process flow for each area as well as how you are planning to handle your information

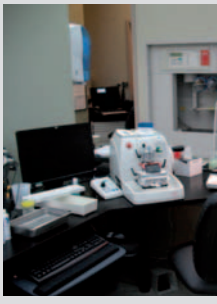
Successful incorporation of LEAN principles



Grossing Area at Catholic Medical Center

Grossing and processing area

Embedding and sectioning areas



flow: ideally paperless with barcoding and specimen tracking through each process step, which will require PC monitors and scanners throughout the laboratory.

Once you have visualized the process flow, take a look at the equipment you are planning to put in the laboratory. Are there instruments that will be shared by laboratory areas? E.g. will the H&E Stainer be used to dehydrate IHC slides as well? The identification of shared equipment will determine where this equipment is situated in the laboratory as it should be accessible from all areas that it will be used for.

With your Value Stream Map in hand which will show you the Takt Time (available work hours / per day divided by customer demand / per day based on your expected specimen volumes) you will know how often you have to sign-out slides in order to meet the customer demand. Be sure to include your growth prediction for the next 3-5 years into the customer demand in order to set the laboratory up for growth. Knowing the Takt Time will then determine how to utilize your equipment (how many processor runs or stainer runs are needed throughout the day) and how many employees you need at what time throughout the day in order to meet customer demand in a timely fashion. Once the number and timing of your staff is known you are able to decide how much equipment will be shared amongst shifts. By now you should have all questions answered in order to start designing the laboratory layout.

Lean Process Flow

As no laboratory blueprint looks the same, the following illustrations are meant to demonstrate the components needed in each area of the laboratory and give helpful hints on how to place them according to a LEAN process flow.

Accessioning area

Every accessioning desk should have a PC with a scanner and a LIS label printer in order to print barcoded labels for the vials which can then be scanned at grossing if needed. The requisition forms should be scanned into the LIS (Fig. 1) and placed onto the network (server) to be accessible for the pathologists, transcription and billing if needed.

The specimens will then be passed to the grossing area in a container holding the standard batch size, ideally through a pass-through window.

Grossing and processing area

The room contains grossing stations, cassette label printers, specimen storage, processors and flammable cabinets for the bulk reagents (Fig. 2).

There should be a clean sink as well as lab coat hangers outside.

The grossing stations are each equipped with a cassette label printer, a PC with monitor, a scanner, a microphone for voice recognition and a digital camera if desired.

Once the specimens have been passed through the window they should be put onto a trolley which will be placed in between the grossing stations.

The PA takes the specimen vial and scans it which generates an automatic printout of the cassettes needed in pre-defined quantities. If the numbers of cassettes printed have to be increased or decreased the PA is able to adjust the quantities immediately in the LIS system, thus reducing the possibility of errors downstream in the process. The grossing is recorded via voice recognition software. The specimens are placed into the color coded cassettes which are placed into the processor racks sitting in a bucket with formalin designated to the rapid processors that they will be placed in. The numerical order within the case is kept.

The rapid processors are utilized several times a day to minimize the batch sizes and achieve continuous workflow.

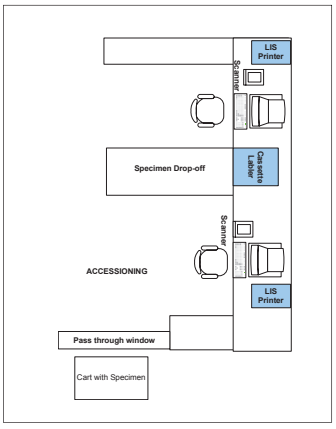


Fig. 1: Accessioning area

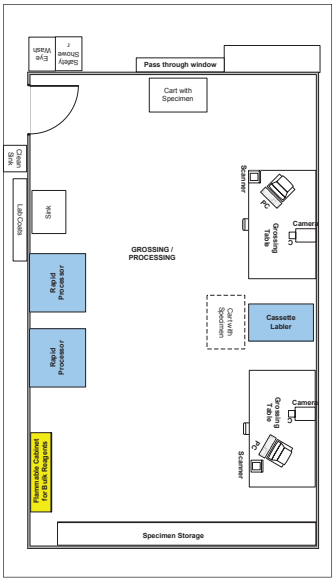


Fig. 2: Grossing and processing area

Staining and coverslipping area

Slide sign out and QC area

Opening of the laboratory in January 2010

All pictures are courtesy of Catholic Medical Center, New Hampshire

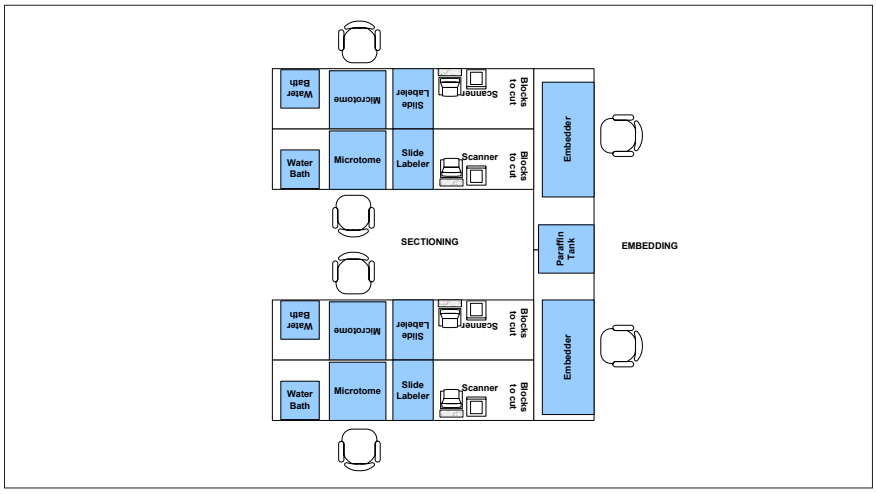


Fig. 3: Embedding and sectioning areas

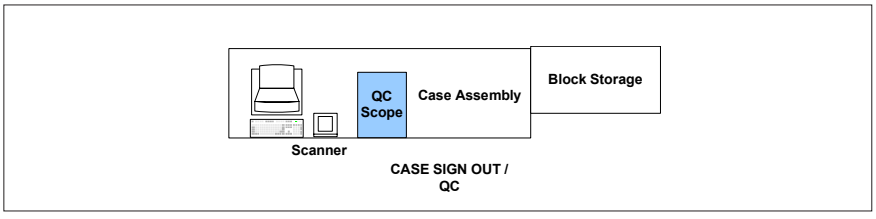


Fig. 4: Slide sign out and QC area

Embedding and sectioning areas

The embedding and sectioning areas are in very close proximity to each other in order to achieve the concept of one case flow or small batch sizes (Fig. 3).

Therefore they should contain the embedding centers, slide labelers, microtomes, water bath, monitors and scanners at each station.

The cassettes that have been processed should be equally distributed amongst all embedding centers. If there are questions at the embedding stage about the case, the cassette can be scanned and the case history can be retrieved from the LIS system.

Once embedded, a complete case or a small predefined batch size will be moved to a microtome station. The embedder should distribute the workload continuously to all microtome stations keeping cases together.

The HistoTech scans the block and the slide labeler automatically prints bar-coded color coded slides according to a pre-defined panel.

The blocks are trimmed and sectioned and put immediately into the H&E stainer rack.

Staining and coverslipping area

This area contains an automated stainer/coverslipper, as well as a sink and the flammable cabinet for the bulk reagents. As soon as a stainer rack is filled with slides the rack is placed into the H&E stainer/coverslipper to achieve continuous flow. Cases are kept together.

Slide sign out and QC area

This area which is located in close proximity to the cover slipper will consist of a microscope for QC, a PC and a scanner (Fig. 4). The slides that have been taken off the cover slipper will be placed into slide folders, checked underneath the microscope and then the slides in the folder will be scanned to sign them out within the LIS.

This should trigger a notification at the pathologist´s PC that there are slides to be read.

The file folders will then be placed in an appropriate location to be picked up by the pathologist.

Ideally the block storage is close to this area as if you process IHC, Special Stains and Re-cuts you will be able to find the blocks you need in this area.

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Case Study for a Lean Laboratory Design

Catholic Medical Center, Manchester, New Hampshire

In October 2008, Leica Microsystems was presented with the opportunity to partner with the Catholic Medical Center (CMC) in order to build and equip a lean pathology laboratory from scratch. The goal was to incorporate LEAN principles into the facility design, the equipment, the processes, the consumables and staffing decisions.

CMC is a 330-bed, full-service healthcare facility located in New Hampshire's largest city, Manchester. It is host to 25 subspecialties, the largest of which is the New England Heart Institute, one of the premier cardiac treatment facilities in New England. The core team members at CMC – consisting of the medical director, laboratory director, laboratory manager, pathology supervisor and laboratory information system analysts, as well as the architect – diligently researched all available vendor options and benchmarked existing lean laboratories. A key factor early in the planning was to incorporate the vendors they would be purchasing the majority of their equipment and supplies from as partners in the project. The pathology supervisor Stephen Feher, who got on board 12 months before the laboratory was scheduled to open, began meeting weekly with Katja Lehmann from Leica Microsystems in order to formulate preliminary workflows and work schedules and review the physical layout and projected equipment placement.

As Feher began to track the types of specimens that were being sent out, preliminary processing schedules were formulated based on expected processing times and the benchmarked times recorded by other institutions for the other tasks associated with a fully functioning pathology lab. Completion of the project was a full six to eight months away, but a preliminary workflow and staffing projection based on workload and workflow began to take shape. The next step was interviewing staff and including the concept of lean staffing and workflow up front in the process. A large part of staff selection would be their reaction and acceptance of a new way of practicing pathology: As a lab without a third shift or weekend work that was capable of producing as much or more than traditional pathology labs. The laboratory opened in January 2010.

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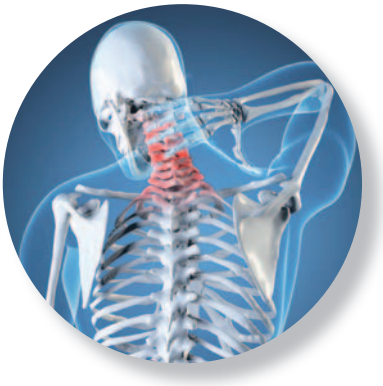

Ergonomics Encourage Concentration in Lab Routine

Body in Balance

Kerstin Pingel, Leica Microsystems

Nobody is the same. Whether large or small, well- or slightly built, left- or right-handed, everyone has different demands of the tool they work with for many hours a day. This is particularly true of laboratory workstations, where routine tasks such as pipetting or microscope or microtome work require a static posture.

Fig. 1: The PhysioCap with a silicone insert weighing 500 grams trains and conditions the neck and spine muscles and encourages the body to automatically assume a good upright posture.

Fig. 2: The Austrian physiotherapist John Ludescher has had his own practice for nine years. He is author of the book "Aufrecht – Bewusst – Stark" (Upright – Aware – Strong) and designer of the PhysioCap.

Occupational medicine studies show that workplaces with optical instruments are particularly taxing on the spine, hand and eyes. Microscopy workstations place far higher demands on the user than the computer screens that receive so much public attention. The combination of sitting at the microscope in a fixed position and repetitive hand movements carries the risk of strain to neck muscles and the upper extremities.

Ergonomically designed workplaces and routines are therefore a prerequisite for wellbeing, motivation and efficiency. The initial investment in ergonomics soon pays off and has long-lasting benefits for all those involved, leading to better results, higher work quality and, ultimately, fewer working hours lost.

Physiotherapist John Ludescher explains how the body can be given optimal support to perform at its best. The Austrian qualified as an physiotherapist in Switzerland and has had his own practice for nine years. He is the author of the book "Aufrecht – Bewusst – Stark" (Upright – Aware – Strong) and designer of the "PhysioCap".

Mr. Ludescher, which parts of the body are subject to particular strain when working with a microscope?

Mainly the cervical spine, the junction between cervical and thoracic spine, as well as the shoulder and neck muscles. The strain manifests itself in symptoms such as tenseness and pain in the shoulder muscles that may radiate into the arms, slipped discs, headaches, tinnitus symptoms and general states of exhaustion. The frequently observed anteroposition of the head also has a negative effect. This leads to an unfavorable position of the first cervical vertebra. Hyperextension of the wrists causes asymmetrical strain on the lower arm muscles, which can result in tendon sheath pain and the so-called "tennis elbow".

What does an ergonomically ideal workplace at the microscope look like?

The body should be in a perpendicular line, i.e. ear, shoulder joint and hip joint have to be in vertical alignment. The first step towards achieving this is to make sure the chair is properly adjusted: In a sitting position, the hip joint should be at an angle of greater than 90 degrees to the upper part of the body. Also, the hip joints should be higher than the knee joints to be able to bend both legs at right angles. This straightens the position of the pelvis, making sitting less tiring. The muscles are in a neutral position and strain is avoided. Finally, when adjusting the inclination of the seat it is important that the pressure of the seat is evenly distributed to the thighs. In a second step, the table has to be set at the right height and the right working distance between the chair and the table must be observed.

After these adjustments have been carried out, it's time for the third step: the position of the microscope is adjusted to enable an upright posture. Depending on the user´s physique, the viewing height and angle of the tube has to be adjusted until he or she can work in a comfortable upright posture and with the correct working distance. Of course, this is only possible with a microscope system featuring variable binocular tubes and flexible accessories. They should also be

easy to handle, as in many laboratories several employees use the same microscope in succession. In this respect, Leica Microsystems provides a pioneering portfolio of products.

That is the best case scenario. And what is everyday reality in a laboratory?

Most people sit down first and then adjust their posture to the microscope, which inevitably leads to posture errors and the types of pain I described.

What else can be done do to counteract physical strain at the microscope?

Extremely important, of course, is physical fitness, a healthy lifestyle and awareness of the body. Because to bring the body into the perpendicular line necessary for relaxed sitting and working, you have to know how it feels when you are in equilibrium. After all, you can't have a look at yourself in a mirror first!

The PhysioCap I designed is useful for this. It's a baseball cap with a silicone insert weighing 500 grams. It gives you the feeling you're balancing a book on your head. This cap trains and conditions the neck and spine muscles and encourages the body to automatically assume a good upright posture. With time, a correct posture is "programmed", as it were. Good results can only be delivered if the body, of which we demand a great deal, is offered optimum conditions. An upright, comfortable posture improves concentration and the quality of work – and makes you feel less exhausted at the end of the day. After all, a successful day doesn't end when you leave the laboratory.

Fig. 3: The Leica DM1000 – DM3000 series microscopes adjust perfectly to the physical needs of individual users.

Contact:
John Ludescher, Physiotherapist
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Focusing on the User

The microscopes of the Leica DM1000, DM1000 LED, DM2000, DM2500 and DM3000 series adapt completely to the user's physique to help maintain a relaxed posture over long periods of time.

A flexibly adjustable or fixed ergonomic 15° viewing angle, various tube lengths and height adjustment elements are extremely important for preventing neck strain.

Because of the symmetrical arrangement of the stage and focus controls, users automatically adopt a natural, comfortable posture. Even after a long session at the microscope, there is no back and shoulder strain.

Leica's DM1000 – DM3000 series microscopes are the only to feature focus controls that can be raised or lowered to match the size of the user's hand, providing a relaxed arm and hand position without the need for supports or improvised props.

Left-handed users can simply switch the controls to the left side of the microscope.

Leica RemoteCare for Constant System Availability

System Maintenance From A Distance

Kerstin Pingel, Leica Microsystems

Most laboratory equipment has to work without interruptions and any faults have to be remedied immediately. Leica Microsystems has come up with a new answer to this requirement: Leica RemoteCare improves system reliability and helps to protect sensitive samples.

"I was rather skeptical at first. But after this emergency where all our valuable samples were rescued and a lot of time and money was saved, I am fully convinced that Leica RemoteCare is a great help to us in our everyday work and a major step in the direction of more safety", explains Antonio Cimino, lab manager at the University Hospital Molinette San Giovanne Battista, Turin.

Proactive procedure

Leica RemoteCare is a monitoring program that keeps a watch on defined hardware and software parameters which are critical for the performance of the system at the customer's site. The system automatically transmits this data from the customer to a server where it can be viewed by Leica's Technical Service. Any changes in the system parameters are communicated both to Leica service staff and to the customer in an e-mail alert, enabling the appropriate action to be taken. "This proactive procedure helps us to avoid downtimes, react more swiftly to faults and even remedy them from a distance," explains Frank Bunge, Director of Leica Microsystems' European Technical Service. In the laboratory sector, Leica RemoteCare is available for the automatic tissue processors Leica ASP200 S and ASP300 S and will be offered for all complex systems of Leica Microsystems launched on the market in future.

Top priority in hospitals: round-the-clock system availability

Constant system availability is a particularly important issue in hospitals, where sensitive patient samples are examined. The following case from Turin shows how useful Leica RemoteCare can be: One Saturday afternoon, the team manager of the Technical Service of Leica Microsystems Italy receives an e-mail via RemoteCare notifying him that there is a fault in the Leica ASP300 S automatic tissue processor in the University Hospital Molinette San Giovanne Battista in Turin. Logging into the customer's system, he sees what has prompted the alert: There is no liquid in the test tube, the samples are in danger of drying out. By the time lab staff notice the fault on Monday morning, the sensitive patient material will have long been irretrievably destroyed and diagnosis will be impossible. The service manager of Leica Microsystems immediately contacts the lab manager, who drives to the hospital and rescues the valuable samples.

"Our Leica RemoteCare service is unique on the market," says Bunge. "Our monitoring program enhances the reliability of our systems and therefore the productivity of our customers."

And this is how Leica RemoteCare works:

Avoiding faults
The proactive monitoring of Leica systems enables changes in parameters to be detected before problems arise. System downtimes can therefore be avoided.

RemoteAlarm
The RemoteAlarm feature notifies both the user and the Technical Service of Leica Microsystems. This technology is used in areas where sensitive material is examined and a system failure can therefore not be tolerated.

Application support
With Leica RemoteCare, Leica's application specialists and customers can discuss any problems right in front of the system without the application specialist having to travel to the customer's site. Instead of spending time and money on travel, the service team can begin solving the problem right away. This increases lab productivity and enhances the efficiency of the products.

Leica ASP300 S Tissue Processor

Simple, Safe and Efficient Tissue Processing

Hermann Ulbrich, Leica Microsystems

In histopathology, consistently high sample quality is of paramount importance – day after day and year after year. The Leica ASP300 S Tissue Processor was specially developed with this mind: Proven and enhanced technology with an innovative user interface and a unique design make the Leica ASP300 S one of the most reliable instruments available for tissue processing.

Quick access to favorite programs

Frequently used programs can be defined as 'favorites' and started with a single touch of the screen. This smart start function also includes other parameters such as an end-time programming option. The user-friendly smart start helps avoid user errors and improves the reliability of operation.

Safety at the workplace

Contaminated air is safely kept in the instrument by an active condenser. The internal air handling system is completed by an activated carbon filter which absorbs any remaining fumes. All reagents (including paraffin) are drained through an external hose system, completely preventing user exposure.

Minimized reagent carry-over

The risk of reagent carry-over is minimized by an improved reagent bottle and module design and a software-controlled, three-stage drain system.

Active paraffin cleaning

Solvent contaminants are safely removed from the paraffin by simply touching a key on the screen. The extraction process ensures efficient paraffin cleaning, which extends paraffin life, improves sample quality and reduces operation costs.

Reagent management system

The improved Reagent Management System (RMS) allows critical data to be assessed at a glance and ensures that all reagents are used in order of cleanliness. The RMS helps reduce reagent consumption and optimizes sample quality.

Tips &Tricks in Sample Preparation

Knife Angle in Microtomy

Charles W. Scouten, Ph.D., Leica Microsystems

To prepare biological tissue for observation under a microscope, the tissue is usually cut in thin slices. Most biological tissue is too soft to cut; the knife would push into it and compress it, even if the cutting edge was very sharp. Therefore, the tissue is either frozen and sectioned in a cryostat or embedded in a hardening material like paraffin or resin, or cut while still soft with a vibrating blade microtome. The correct knife angle is the subject of much misunderstanding, misleading experience, and incorrect information passed between microtomists, but in fact can be logically derived.

Ideal versus compromise

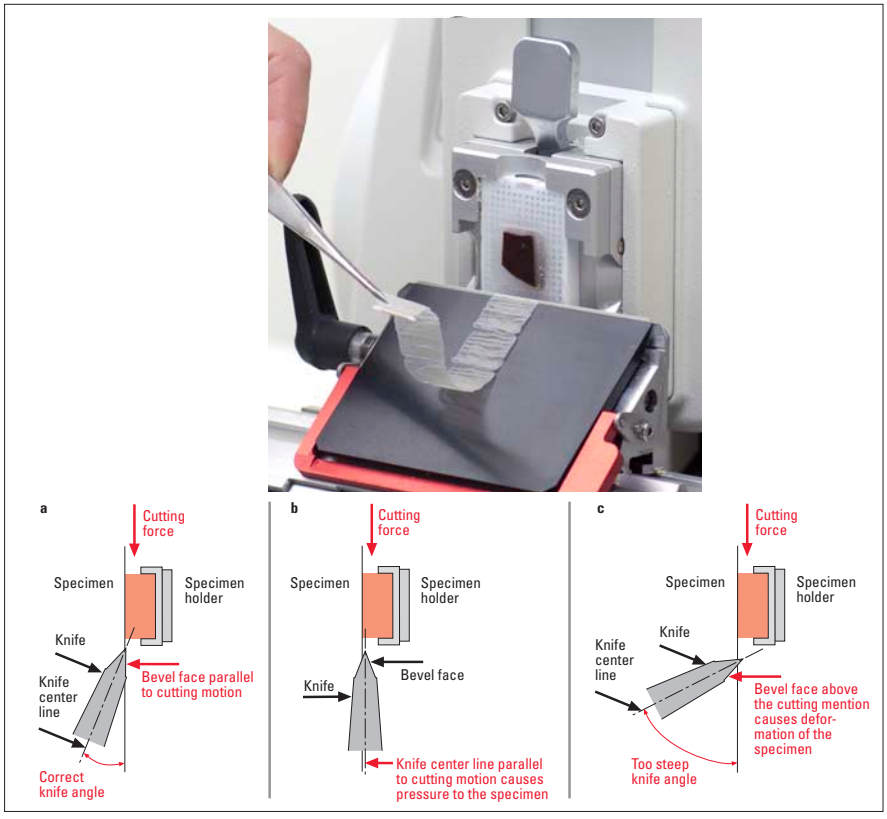
The ideal knife for sectioning any material in any microtome, regardless of specimen hardness, would be an infinitely thin plane. This would be oriented parallel to the plane of the cutting movement. Unfortunately, infinitely thin planes are hard to come by, and in fact are found only in geometry books.

Real knives are a compromise, or several compromises, between physics, available materials, manufacturability, and cost. They must have measurable thickness to be held stable during cutting. So the leading edge must be made thinner than the main body of the knife, in a wedge shape (Figure 1), to enable both cutting and physical inflexibility. All microtome knives, whether resharpenable or disposable, have a wedge shaped part.

The entire knife could in theory be a smooth wedge, with gradual slope to the leading edge. However, sharpening the knife would then require removing a layer from at least one whole face of the knife. In practice, there is always a final bevel at a steeper angle for about a millimeter back from the cutting edge. The final bevel may be symmetrical on both sides, or not. The final bevel helps with sharpening and resharpening, only the bevel face(s) surface has to be removed to sharpen.

In a microtome, the center line through the cross-section of the knife, as shown in Fig 1a, is always positioned at an angle to the main direction of motion, not parallel to the direction of motion as it would be for an ideal infinitely thin knife. This is necessary because of the bevel. The angle is required because the knife is wedge shaped in cross section (at least the beveled leading edge of it). This compromise with the ideal knife has two negative consequences.

Fig. 1: **a** the correct knife angle, **b** too shallow, **c** too steep



Consequences of too shallow an angle

Suppose the knife is held so that the plane of motion (of the knife or specimen) is parallel to the centerline through the wedge, as would be appropriate with an ideal knife (Fig. 1 b). The face of the bevel on the specimen side of the knife would then be pressed hard against the specimen, increasingly so with more cutting movement, and apply compressive and forward pressure to the specimen. This is never good, and there are several possible consequences that depend on the tissue properties, knife properties, and on how well the specimen is adhered to the specimen holder:

- If the tissue is soft, the section will be cut, but the block face where the next section will come from will be compressed down and forward, abraded,

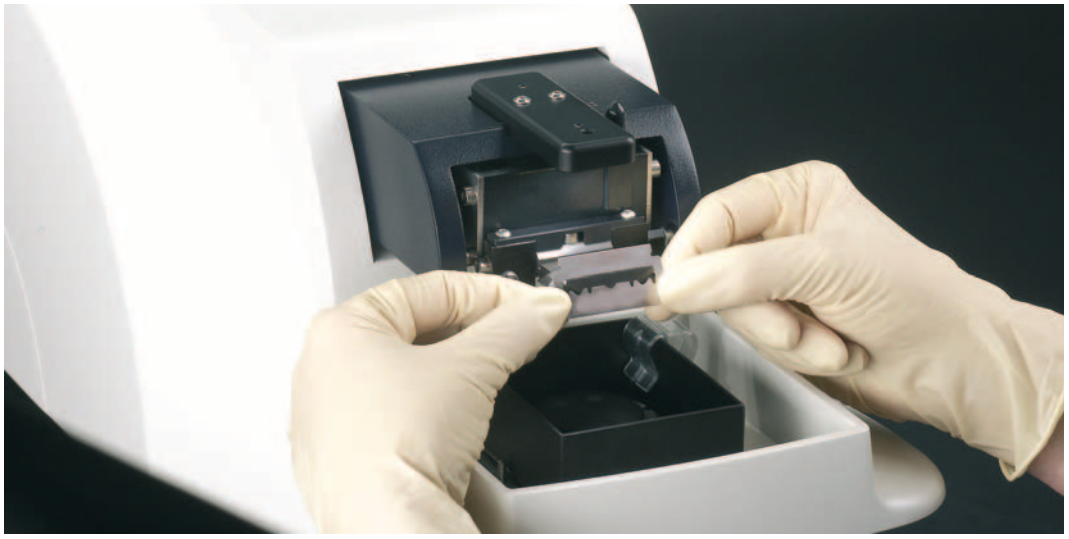


Fig. 2: The Leica VT1200 semiautomatic vibrating blade microtome is designed for sectioning fixed or unfixed specimens in Neuropathology (fresh brain slicing) and Neurophysiology (patch-clamping). The instrument is recommended for users who wish to manually select the desired section thickness prior to cutting each section. The vertical deflection can be measured by using the optional measurement device "Vibrocheck".

Fig. 3: Designed for fully motorized sectioning of both paraffin- and resin-embedded specimens, the Leica RM2255 supports a broad spectrum of applications; in routine and research laboratories; in histology; in industrial materials and quality control. Its two-in-one design concept, which allows motorized and manual sectioning, provides reproducible high-quality sections.

The new Leica RM CoolClamp mounts easily to any Leica RM2200 series microtome and maintains block temperature at 20 °C below ambient. With each block held at the ideal temperature, you'll find it easy to cut high-quality sections for routine, special and IHC/ISH staining.

and damaged. The most common result is alternating thick and thin sections (this can also occur if either the knife or the specimen holder is not tightly secured and can move under pressure).

- If the tissue is hard, or a vibrating blade is used, the result of the pressure may be not to compress the tissue, but to flex the knife upward. If the knife can be flexed, it may "skate" up out of the tissue somewhere in the interior of the intended section, separating partial fragments, or make a wavy pattern on the block surface, called Venetian blinds, where the knife is deflected up, then springs back. Some degree of waves can happen even with correct knife angle, due to specimen compression in front of the knife.

- Excessive forward push on the specimen block could cause the specimen to break off the specimen holder.

The lesson here is that the knife always needs a high enough angle to prevent the trailing part of the lower bevel face from applying pressure to the specimen block.

Consequences of too steep an angle

Suppose instead that the knife is raised to a steep angle between a center line through the knife cross section and the axis of movement, so that the lower face of the wedge no longer pushes down and forward on the block (Figure 1c). However, the upper face of the wedge is always pushing on the uncut specimen above the cutting edge. This bends the section very sharply up at the line of cut as it is separated from the specimen block. As with any object with any thickness being bent, the lower surface of the section at the bend will be stretched and some separations will occur. The upper surface will be compressed. If the deformed specimen does not spring back, the tissue

will roll into a tight roll. Even if it does spring back, and is prevented from rolling, the section will be altered. It is never good to bend the section any more that it has to bend given the need to push the wedge in. There are again several possible consequences, depending on the specimen and knife properties:

- If the knife is flexible and the specimen is hard, the knife may bend down and dive down into the specimen block.
- If the specimen is hard, it may have shatter, sometimes called chatter, lines running parallel to the knife edge, where the hard section was sharply bent and broke.
- If the specimen is weakly connected the section may look more like scrapings than a smooth section.
- A soft section may roll up in a tight roll, taking the shape given it at the line of cut.

What is the correct knife angle?

As a general principle, excessive bending of the section at the cut line is never advantageous in histology or material sectioning. However, errors of too shallow an angle are more damaging to the specimen than errors of too steep an angle. This leads inevitably to the conclusion that the correct knife angle should always be set in the following manner: Position the lower bevel face parallel to the specimen block and the plane of motion. Then raise the angle slightly (1/2 degree if you can manage such a thing) above the bevel angle to avoid having the lower bevel face slide over the specimen block and possibly produce friction damage. The correct knife angle positioning should be consistent regardless of the type of microtome, or any specimen property.

The consequences of incorrect knife angle will vary because of differences in specimen types, fixation and processing qualities and knife flexibility. Knife and disposable blade properties must also be considered because they can be manufactured with different profiles and angles. The correct knife angle is a property of the type of knife and the final bevel, and may be different on knives from different manufacturer's and may change after re-sharpening. To reduce the likelihood of changes in knife angle with sharpening, the knife should always be professionally sharpened.

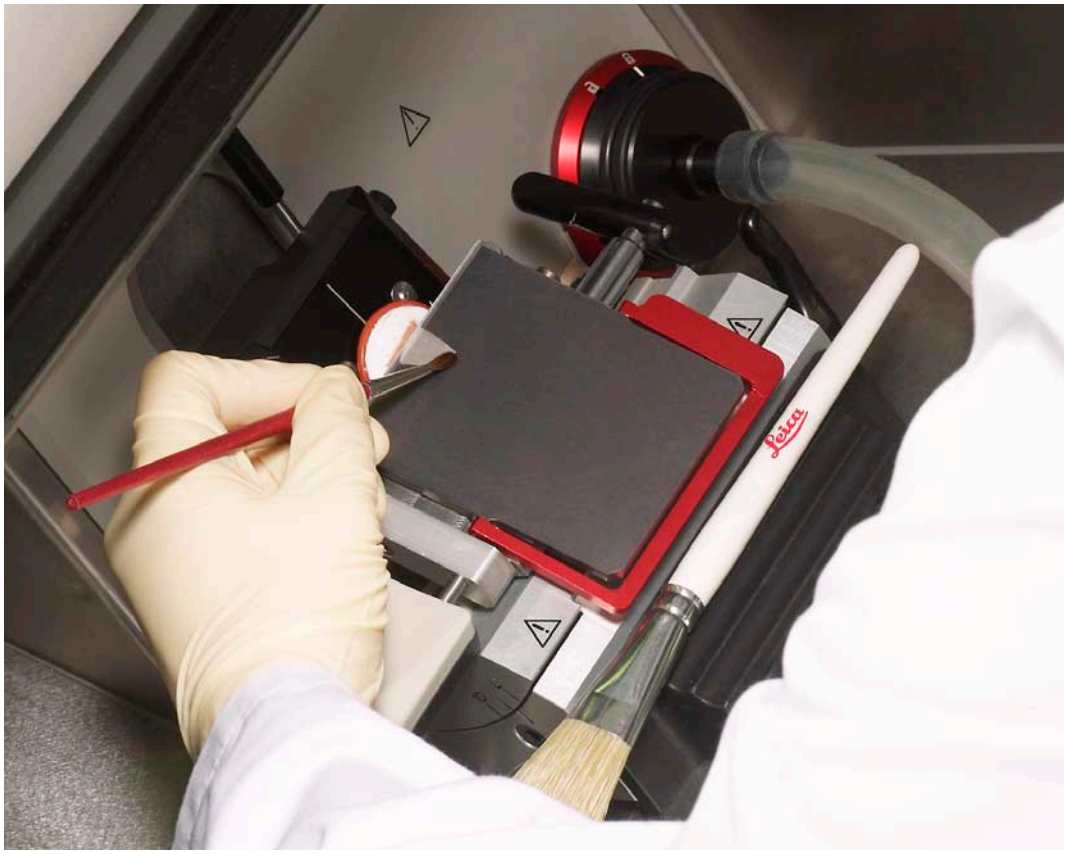


Fig. 4: The Leica CM1950 cryostat is a highly adaptable platform that can be tailor-made for each laboratory. By starting with the standard instrument and choosing from a range of options, every laboratory can have the optimal clinical cryostat for their individual needs. Innovation and human-oriented features provide a cryostat with a new level of performance.

Leica Microsystems' Complete Histology Product Range

Total Histology Solutions

Total Histology brings together products, quality and support. It's the complete solution that helps you advance workflows, enhance diagnostic clarity and deliver what really matters – better patient care. Leica Total Histology is all elements of tissue-based pathology brought together – instruments and consumables, history and education, support, and innovation. Now, instruments and consumables form complete systems, each individual step is considered part of a single inclusive process, and one partner can support the entire histology workflow.

Quality
Quality is fundamental; it's never an option. The first thing built into any Leica product or service is the quality that you need to deliver clear and accurate staining so pathologists can confidently and quickly make accurate assessments.

Innovation
It's the Leica Microsystems tradition to work closely with customers to provide solutions to real problems. The results: over 100 years of histology firsts that have made a real difference to histology.

Knowledge-based sales
All Leica sales staff have the knowledge and expertise to find the right solution for your laboratory.

One contact, many options
With Leica Total Histology, a single call can deliver exactly what you need, from a single product to a complete solution for your entire histology workflow.

Education
As knowledge and sharing is central to Leica Microsystems, we foster scientific education through product training, practical in-lab support, seminars and the popular Scientia series of educational publications.

Broad range
A broad range means we always look at your entire process – never an individual product in isolation. A broad range also means tailored solutions.

Leica Total Histology means comprehensive histology knowledge creating totally cohesive systems. Now instruments, reagents and consumables work together at each histology step, and each histology step builds towards the clear and consistent slides that pathologists expect.

New AirChek Dosimeter Badges

Monitoring Hazardous Substances

Neil Haine, Ph.D., Leica Microsystems

Laboratory personnel, even with the greatest of care and with ventilation systems in place can, under certain circumstances, be exposed to small amounts of chemicals such as formaldehyde, glutaraldehyde and xylene when they are at work. If these 'hazardous substances' are not properly monitored and controlled they may cause ill health if taken into the body through respiration or skin absorption. To help employers address the problems of effective monitoring, Leica Microsystems now supplies the AirChek Dosimeter Badge for accurate and easy recording of individual exposure.

AirChek Dosimeter Badges are available for many chemicals, e.g.:

- Formaldehyde
- Glutaraldehyde
- Xylene
- Toluene
- Isopropanol

With employer responsibility towards employee health and welfare becoming increasingly topical, employers should be aware of their legal responsibilities. Governments have generally set out legal standards and workplace exposure limits for hazardous substances at work and require employers to carry out suitable and sufficient risk assessments including the monitoring of the exposure levels.

Statutory requirements

There are many chemicals listed as toxic substances and these must be controlled below safe legal limits. In the UK for instance, Occupational Exposure Limits (OELs) are included in the Health and Safety Executive Publication EH40, which is updated annually.

In the UK, the principal regulations governing substances hazardous to health are 'The Control of Substances Hazardous to Health Regulations 1999 (COSHH)'. Under these regulations OELs are defined as Workplace Exposure Limits (WELs) or concentrations of hazardous substances in the air averaged over a specified period of time called a Time Weighted Average (TWA). Two time periods are used: long term (measured over 8 hours) and short term (15 minutes). Short term exposure limits (STELs) are set to help prevent immediate effects of exposure to harmful substances.

In certain circumstances the exposure must be monitored to ensure that WELs are not exceeded and to check the effectiveness of any control measures put in place. Similar regulations apply across the European Union although the actual limits themselves can vary.

Monitoring procedures

The frequency of sampling will depend on the factors considered by a risk assessment, including: the processes and substances present in the workplace, the control measures used, how they are tested and maintained and the concentration of the substance. Where monitoring is required for continuous processes or regular activities, it should be carried out at least once every 12 months, although for some specific substances and processes more frequent monitoring is required. Monitoring should also be carried out when a process changes significantly to ensure that control measures are still effective. For infrequent activities that take place at intervals exceeding 12 months, monitoring should be carried out during the activities concerned.

Where groups of employees are being exposed to similar risks to health, sampling may be carried out on a representative group basis. Exposure to mixtures requires careful assessment of health effects and the appropriateness of control standards as the effects to health can be complex.

Information recorded

For respiratory exposure, methods involving sampling within the breathing zone of the worker are most effective and provide a personal record of actual exposure that can be retained as part of an employee's personnel records. A record should provide sufficient information to determine:

- when the monitoring was done and what the results were;
- what monitoring procedures were adopted, including the duration; and
- the locations where samples were taken, the operations in progress at the time and, in the case of personal samples, the names of the individuals concerned.

The information should be readily retrievable, easy to interpret, and comparable to any other health records required.

Simple badge – effective monitoring

The AirChek Dosimeter Badge from Leica Microsystems was developed as an inexpensive and unobtrusive device to monitor toxic chemicals. The badge is simply clipped onto the work clothes at a point as close as possible to the breathing zone for the duration of the monitoring period. This will ensure that the TWA occupational exposure will be impregnated onto the badge 'sensing' material and the badge can then be returned for analysis.

The badges provide the 8-hour continuous sampling or the 15-minute STEL for personal monitoring that is required under, for example, UK government legislation.

Within a few days of the badge being returned, a laboratory test result will be forwarded to the employer providing a permanent and personal record of any individual's exposure. The tests are carried out in accordance with UK Health & Safety Executive recommendations & requirements as well as those for OSHA & NIOSH in the USA. The report itself gives clear, concise information that can be easily compared to the published WELs.

Some monitoring systems offer only a 'spot-check' at a particular point in time or for a particular area within the working environment. Leica's AirChek Dosimeter Badges provide a much more accurate indication of an individual's exposure throughout the duration of a working day (8 hours) or during a specific task (15 minutes) and a wide selection of badges is available to monitor a variety of chemical vapours.

Some recent court cases have resulted in employees being awarded substantial damages against their employer because the employer could not offer evidence that adequate precautions had been taken. The AirChek Dosimeter Badges help to ensure that evidence is available and that the health of staff is protected. For further information on local statutory health and safety regulations we recommend you contact your local Health and Safety regulatory body.

To monitor the individual exposure to toxic chemicals, the AirChek Dosimeter Badge is simply clipped onto the work clothes at a point as close as possible to the breathing zone.

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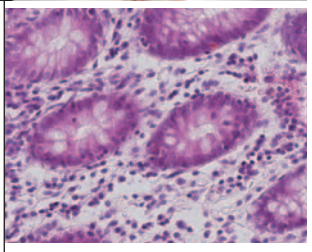

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