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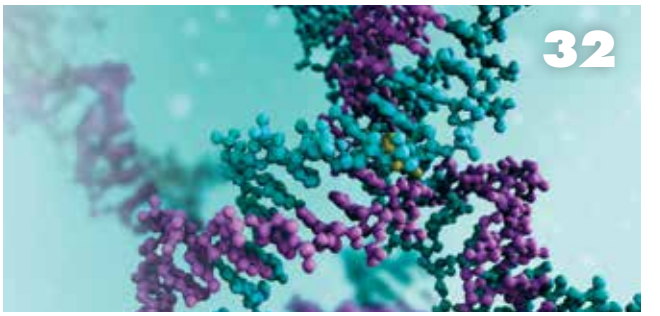

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If all goes according to schedule, by the time you read this, the new design for the Lab Products pages on LabManager.com will be live. Our aim for this redesign is to streamline the numerous sections on each page to a more manageable number as well as improve the look and functionality of the pages. We hope the new design makes it easier than ever for you to find the latest lab product releases as well as information and resources for each product category. We welcome any feedback you may have on the new design, as we plan to add further updates and refinements to the site as necessary.

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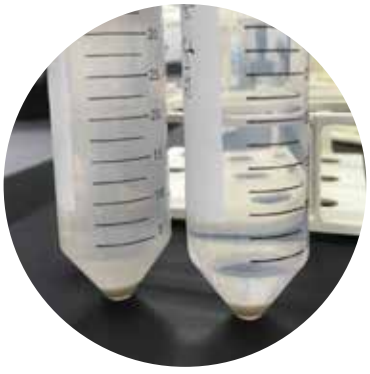

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gentle reminders

As a manager it's sometimes easy to get into a rut or even fall prey to bad habits when it comes to doing your job. You know you could do better at communicating with your staff, addressing larger business issues, or thinking more strategically. However, defaulting to lazier management practices happens to the best of us. Which is why it's necessary to shake things up by revisiting old ideas with a fresh perspective, talking to other lab managers about their challenges and best practices, and getting out of the lab to attend a management seminar or two. Ideas don't need to be revolutionary—in fact, most management theories aren't. We all just need to be reminded of basic management principles we once learned, but may have forgotten.

This month's cover story will hopefully provide that gentle reminder of what being a good lab manager is all about. For cover story author Elizabeth Sandquist, that involves having a plan for where your lab is going, organizing projects, timelines, and budgets, helping your staff be more creative and productive, and keeping an eye on the big picture. "While lab members need technical skills to complete individual experiments, it is the lab manager's job to ensure that all experiments are aimed toward a common goal. The ability to see the bigger picture allows lab members to evaluate a project's progress and determine future projects," reminds Sandquist.

And lest you forget how important good management is, there's this: "For the type of research we do, it turns out management is critical to success because we work as a team and it takes a lot of coordination and dedication. It's an unusual enterprise and it's not for everybody. It takes unusual people to put in that much effort toward something that doesn't give you instant gratification." This is Donald Umstadter, principal scientist and director of The University of Nebraska-Lincoln's Extreme Light Laboratory (ELL), speaking about his research in this month's Labs Less Ordinary (page 14). "Managing those lab members is an extremely important part of the ELL's success," he says, though he admits it can be a challenge as management is not typically part of physicists' or professors' education.

And neither is networking, but that too is what's required these days for both research and professional success. "Most everybody understands there are a variety of benefits to knowing other professionals in their fields—especially in the sciences, where collaborations could be key to further advancing a field," says author Sara Goudarzi in this month's Leadership & Staffing article, "Making Connections" (page 24). As for the fear of awkward introductions and uncomfortable silences in face-to-face meetings, the article provides time-tested techniques for getting around that and the reminder that online social media platforms have created many new opportunities. "Through these time-tested methods, lab professionals are sure to be able to extend their networks. However, with the advent of technological networking, more avenues are now available for managers to get to know, and keep in touch with, their peers," says Goudarzi.

In addition to our management refresher course and networking recommendations, this month's issue also examines fragment-based methods for drug screening, forensic proteomics, the application of LC-MS-MS and GC-MS for water quality monitoring, advances in imaging techniques, and much more. We hope you find all of the offerings useful and inspiring.

Best,
Pam

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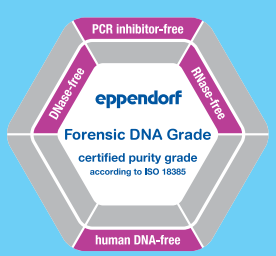

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LAB MANAGEMENT FUNDAMENTALS

TIME-TESTED TIPS FOR STEPPING UP YOUR MANAGEMENT GAME

By Elizabeth Sandquist, PhD

Do you ever feel you were unprepared for a career as the head of a research lab?

You chose the research profession because you were fascinated with the world around you and wanted to discover on a molecular level the ways in which life exists. Additionally, you wanted the freedom to choose your own field of research and study what interests you most.

You long to be at the heart of the lab—directing experiments, analyzing data, and writing papers—but you find yourself caught up in other tasks—ordering reagents, attending yet another meeting, doing anything but bench research.

You have found that being the head of the lab is more than just making big discoveries; it is about managing a small business. Lab-management skills, while used every day by scientists, are not directly taught to young scientists. Rather, they are learned secondhand. While much can be learned from this follow-by-example approach, it has its limits.

Lab management can and should be learned in a more directed manner.

"Laboratory managers are often promoted from the ranks of the technical staff," says Rodney Forsman, the past president of the Clinical Laboratory Management Association and an assistant professor emeritus at the Mayo Clinic College of Medicine in Rochester, Minnesota. "If an individual has the capacity to learn the science of laboratory medicine, they can learn the necessary management skills, given the desire and aptitude to do so."

Management skills are important for science careers of all types. Whether you work at the bench or away, the ability to organize your work and supervise those under you is critical.

Management can be divided into four main categories:

- Planning allows a lab manager to know where the lab is going.
- Organizing is also an important job for a lab manager, because he or she determines who does which project and technique, manages the timelines and budgets for multiple projects, and keeps current with research in the fields.
- Leading is extremely important for a lab manager, because it often sets the environment and pace of the lab. Good leadership can inspire lab members toward productivity and creativity and help members work together.
- Controlling a lab involves the evaluation of lab members' and projects' progress and the ability to correct problems as they arise.

Planning: Considering the big picture

With all the responsibilities that lab management entails, it is easy to make sure the t's get crossed but lose sight of the bigger goal.

A common suggestion from the experts is to have a five-year strategy. In a study by McKinsey & Company, all successful, thriving labs utilized three- to five-year plans.

While lab members need technical skills to complete individual experiments, it is the lab manager's job to ensure that all experiments are aimed toward a common goal. The ability to see the bigger picture allows lab members to evaluate a project's progress and determine future projects. A five-year plan allows you to gauge the progress of your research and keep it goal oriented.

Similarly, a mission statement can guide a lab and keep it on track. Reminding yourself that your mission is, say, children's health, helps you recognize what tasks will help you fulfill your plans and be more productive.

Write a mission statement that will help you and your lab members remember, when things get tough, why you are in science and why your project is important.

Also, scientists love to ask questions, but sometimes that can lead researchers down rabbit holes. A mission statement can guide you in experiment planning so that time is not wasted pursuing trivial or tangential research.

Organizing: More than a clean desk

Organization takes a number of forms in lab management. Time, people, and your physical lab space must be organized and orderly for research to run smoothly. There never will be enough time in the day to complete all the tasks you hope to accomplish, so it is important to know when to say no.

Lab meetings are a great way to help keep a group of people organized and focused on their goals. Meetings with the whole group allow lab members to remain informed of events within the lab. They also can be a good forum for brainstorming and troubleshooting.

The McKinsey & Company study of successful labs also found that top labs have regular lab meetings, both formal and informal. One-on-one meetings also are important for both the lab members and the manager, so experiments and issues can be discussed in greater detail.

However, lab meetings can become an inefficient use of time if they are not organized. Having a meeting agenda can keep conversations on track and avoid the need for multiple meetings about a single issue. Records of lab meetings also can be used to measure research progress.

"It is the lab manager's job to ensure that all experiments are aimed toward a common goal."

Leading by design

Many scientists and managers noted that not all successful leaders are the same. The first step toward reaching your leadership potential is to recognize your leadership style. There are multiple resources online that allow you to recognize and analyze the way you lead. Then you can focus on the strengths and weaknesses of that leadership style and work to improve it.

Additionally, you can compare the type of leader you actually are to the kind you would like to be. "It is advantageous to identify a successful mentor who can not only be a model for your behavior, but also a sounding board for issues you may not have dealt with previously," Forsman says. "The mentor should have experience beyond the laboratory, especially in dealing with organizational protocol and key individuals outside the laboratory."

Jon Lorsch, formerly a professor of biophysics at the Johns Hopkins University School of Medicine and now director of the National Institute of General Medical Sciences, suggests that you optimize your management style for each lab member. "You cannot motivate or help everyone in the same way," he says. "For example, some people respond well to a lot of attention. Other people like to have more time to think about data or their next experiment. You need to be able to modulate your style to optimize it for each person in your lab."

Richard DeFrank, an associate professor of management at the University of Houston C.T. Bauer College of Business, emphasizes the importance of lab members knowing you are involved and available. One way to achieve this is to walk around. Every day, make an effort to walk around the lab and visit with each lab member.

On a related note, many people emphasized that lab managers should walk the talk. In other words, do what you say. This action builds trust and respect from colleagues and fellow scientists. If you desire staff to be in the lab from 8 to 5, they are far more likely to do so if you are there from 8 to 5.

Most of the experts emphasized the importance of listening. A good leader not only directs lab members and tells them what to do, but he or she also listens to his or her employees.

"Make sure you are not the person doing most of the talking at lab meetings," Lorsch says. "If you are, there is a problem." Instead, he suggests that you empower senior members of the staff to teach and mentor junior members.

Taking time to listen is also important because a lot can be gained from your lab members. One way to do this is to organize brainstorming sessions. "This gets creativity flowing, empowers people to think about new research directions for themselves and the rest of the group, and often generates good ideas," Lorsch says. Not only does this make lab members feel appreciated, but it also provides them with a learning experience. Most importantly, it gives you a different perspective on your research than you would have if you worked in isolation.

Lastly, know when to relax and have fun. Taking time to celebrate as a lab is great for morale and can act as an incentive to reach lab goals. Science is full of disappointments, and perseverance is essential for survival. Taking time to relax and enjoy your accomplishments will give lab members and you the energy to continue. "Have a sense of humor," Lorsch says. "This is probably the most important advice I can give."

Controlling: Making sure your employees succeed

Managing a lab means that there are times when things go wrong and you are expected to fix it.

"Managers often lament that 'all problems come in on two feet,' which highlights the importance of honing your people skills," says Forsman.

One of the best ways to prevent issues with employees is to be clear about standards and expectations from the start. Every lab member comes from a different background. Most of the issues rise from a lack of communication about expectations. Without clear expectations, you cannot expect lab members to do something just how you like it. It is equally important for lab standards to be maintained, or they will not be followed.

DeFrank and Lorsch both suggest motivating lab members through rewards rather than fear. "When people are doing well, make sure you tell them so," Lorsch

says. “When things are going slowly, make sure you give encouragement along with advice.” People are more likely to be productive and create high-quality work when they are happy and working toward a goal rather than fearing punishment.

Lastly, try to give lab members a sense of control over their work. A sense of pride and ownership can go a long way to motivate employees, while freeing you to spend time on other issues.

The key to returning to the work you love, science, is to manage your lab well through planning, organizing, leading, and controlling. It may take some work, but the payoff will be rewarding to you and your lab members. Remember: if you can learn science, you can learn lab management.

***Elizabeth Sandquist, PhD**, is a Howard Hughes Medical Institute-supported postdoctoral fellow at Iowa State University where she coordinates the Freshmen Research Initiative, a program that supports introductory course-based research experiences. She also conducts neuroscience research in the department of Genetics, Development and Cell Biology. Elizabeth can be reached at esandq@iastate.edu.*

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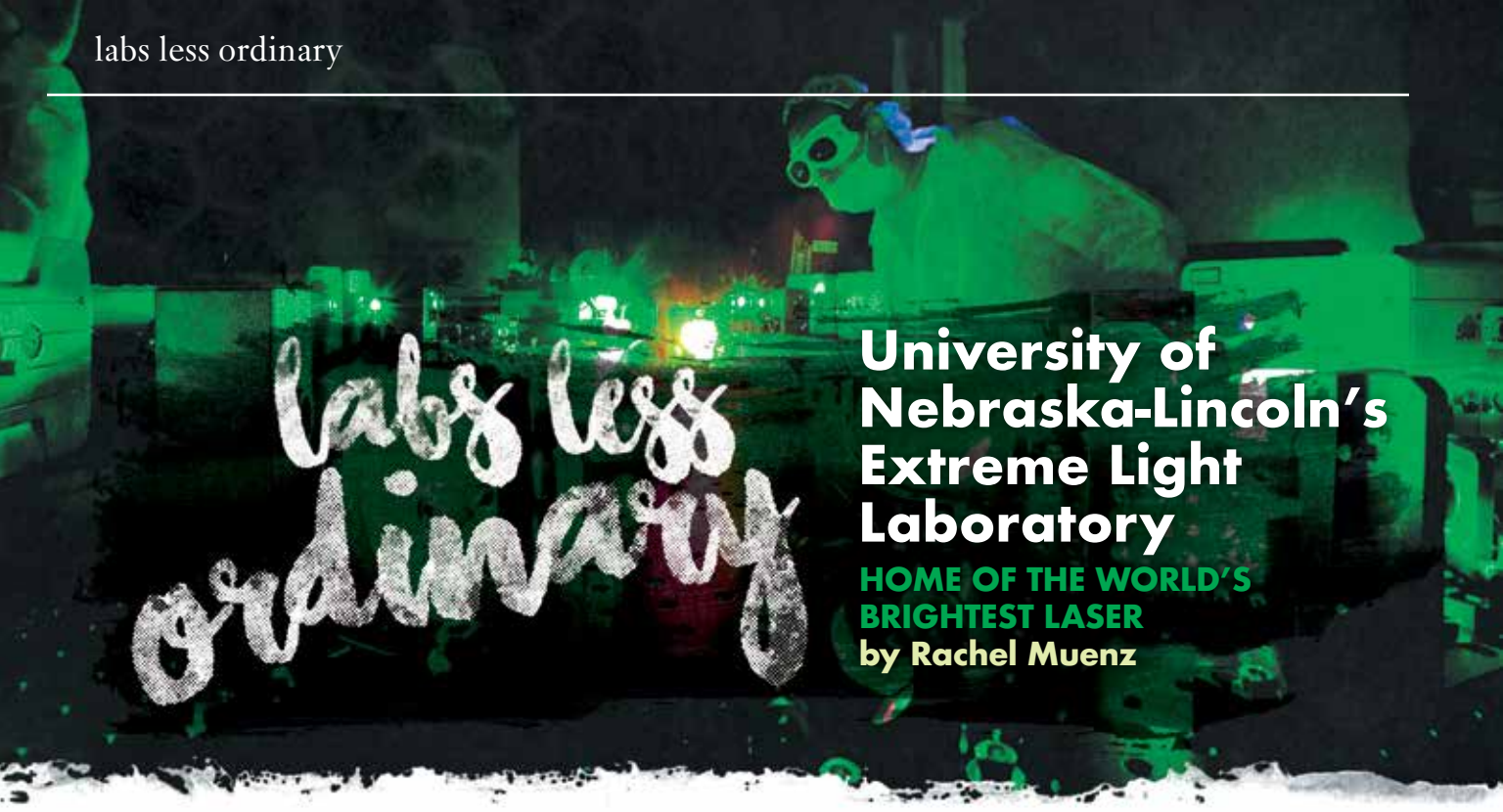
TOP 10 LAB MANAGEMENT TIPS

- You can learn management skills.
- Have a five-year plan for your lab.
- Set clear standards and expectations.
- Optimize your management style for each lab member.
- Listen to your lab members.
- Walk around the lab daily.
- Learn when to say no.
- Be prepared when small amounts of free time become available.
- Get to know the people at your institution who can help you.
- Celebrate successes with your lab.



University of Nebraska-Lincoln's Extreme Light Laboratory

HOME OF THE WORLD'S BRIGHTEST LASER

by Rachel Muenz

While scientists in fiction often use lasers for evil, researchers in the real world use them to help humankind. The University of Nebraska-Lincoln's Extreme Light Laboratory (ELL) is home to one particularly unique laser that could benefit us in many ways.

Diocles, named after the inventor of the parabolic reflector, recently set the record for the world's brightest laser. In a study published on June 26, 2017, in *Nature Photonics* (https://goo.gl/PuWPN4), principal scientist and ELL director Donald Umstadter and his team achieved that record to gain new insights into how extremely bright light scatters. The properties of the X-rays created in that experiment could have important applications in a variety of areas, including cancer diagnostics and materials research.

"It really changes the physics of how we see things in very extreme light conditions," Umstadter says.

Other key research at the lab is focused on miniaturizing synchrotron X-ray light sources, which produce much more powerful and higher-quality X-rays than the machines found in hospitals. However, in order to produce those high-quality X-rays, these synchrotrons must be massive—essentially the size of an entire building. Funded by the National Science Foundation, Umstadter and his team are looking to improve a new generation of laser-driven electron accelerators to shrink those light sources down to a more manageable size. He explains that the acceleration gradient of such laser-driven accelerators is around 100,000 times greater than that of a conventional accelerator, meaning they reach a given electron energy in a distance that's 10,000 times shorter.

▲ A scientist at work in the Extreme Light Laboratory at the University of Nebraska-Lincoln, where physicists using the brightest light ever produced were able to change the way photons scatter from electrons. Photo credit: University of Nebraska-Lincoln Communications

"That allows us to shrink these huge machines that exist around the world to a size that could fit inside a hospital or university lab, and we think, potentially, could fit in a truck that could be moved around," he says. That means higher-quality X-rays could become attainable for academic research and diagnostic applications.

> "There's a lot of creativity involved that probably many people don't appreciate."

"The ability to see much smaller features will enable people to detect cancer at an earlier stage and, potentially, to treat cancer," says Umstadter, adding that to take an X-ray, their light source also deposits a dose of X-rays that's 10 times smaller than conventional machines.

The ELL itself, including office and lab space, is around 4,000 square feet, with 12 people in Umstadter's research group made up of a combination of graduate and undergraduate students, technicians, postdocs, and research scientists. Other faculty besides Umstadter also use the lab's lasers for their own research. Managing those lab members is an extremely important part of the ELL's success, Umstadter says, though he admits it can be a challenge as management is not typically part of physicists' or professors' education.

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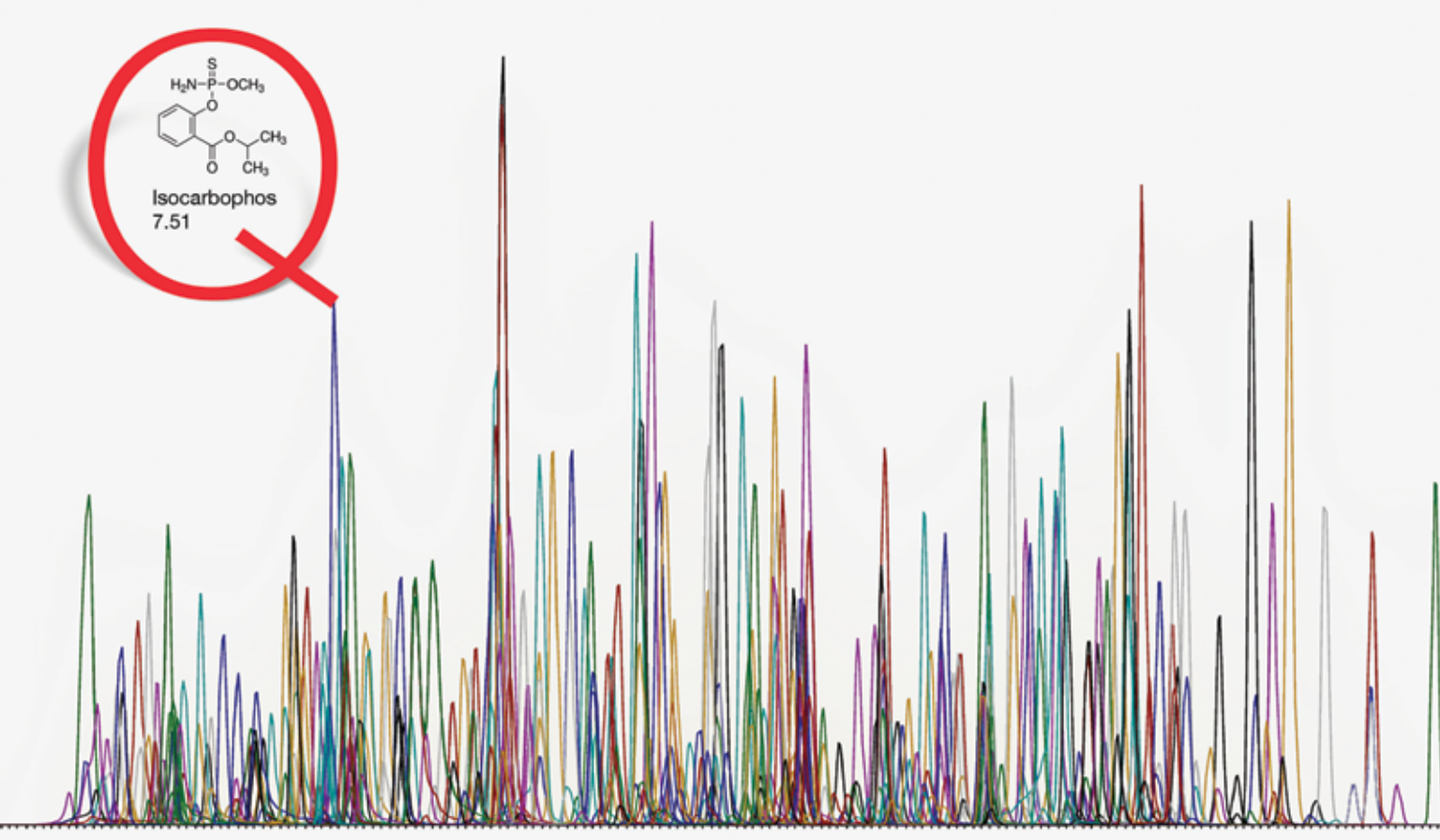

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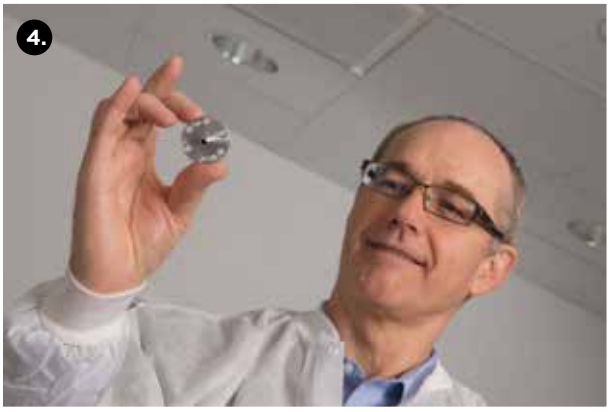

"For the type of research we do, it turns out management is critical to success because we work as a team and it takes a lot of coordination and dedication," he explains. "It's an unusual enterprise and it's not for everybody. It takes unusual people to put in that much effort toward something that doesn't give you instant gratification."

Working with such powerful lasers also involves some unique precautions. Eye protection, as with other laser systems, is obviously a must, but researchers must also wear hairnets, breathing masks, and other protective clothing to protect the lasers themselves.

"We're doing experiments at power levels that are so high that they will vaporize the dust that gets on any of the optical elements, like the lenses and the mirrors, and that can damage them over the long term," Umstadter explains. While the lab isn't a full clean room, it's kept clean enough to prevent such dust damage, and researchers can also precisely control the temperature of its rooms. Chilled water cooling systems for some of the lasers' optical elements keeps them at a steady temperature, and vibration dampening systems in the optical tables ensure their laser systems stay properly aligned even when large trucks or trains are passing nearby.

A challenge in terms of the basic science is that laser research is something of a "hot topic" in physics today, meaning there's a lot of competition, Umstadter says.

"There are a lot of competitors out there who are trying to make the discovery before we do, so the big challenge is to be organized well enough that you can execute fast and be the first to get the results and get them published," he explains.

He adds the challenge with the applied research they do is to bring ideas from the lab to the "real world" and get them to the point where they are mature enough to have a real impact:

"It's particularly challenging with these more-advanced sources because they're relatively new and there [are] tens of thousands of these conventional sources already in use. There is a lot of . . . disruption associated with having something different."

1. & 3. The University of Nebraska-Lincoln received nearly $2 million in federal stimulus funds from the National Science Foundation for renovations to expand its Diocles high-power laser research capabilities. The $1,825,345 grant enabled UNL to renovate the sub-basement and basement of Behlen Laboratory. Photo credit: Craig Chandler, University of Nebraska-Lincoln Communications. **2.** The new Diocles Laser Lab under construction in Behlen Hall, October 1, 2013. Photo credit: Craig Chandler, University of Nebraska-Lincoln Communications. **4.** Donald Umstadter, director of the Diocles Extreme Light laboratory. Photo credit: Greg Nathan, University of Nebraska-Lincoln Communications. **5.** Dr. Umstadter adjusts a mirror used to focus the Diocles Laser. The mirror is parabolic. Greek philosopher Diocles, whom the laser is named after, invented the parabolic mirror in 200 B.C. The same mirror is used in UNL's 21st century laser. The photo is shot through a glass viewing port on a vacuum chamber in which experiments are performed. Photo credit: Erik Stenbakken Photography

To counter those research challenges, Umstadter and his team are trying to stay in the lead in developing the technology, as well as protecting their intellectual property by patenting their ideas through the university. They're also getting government grants to help develop the technology to a point where the private sector would be interested in investing in it.

However, handling new challenges every day makes the work exciting, Umstadter says, adding that the creative process involved is what he enjoys most about working in the lab. "There's a lot of creativity involved that probably many people don't appreciate that goes into taking ideas from just a thought to something real."

For the future, Umstadter says the ELL is continuing to focus on staying ahead of the pack in high-intensity laser research. At the same time, they'd like to expand the facility to allow scientists from the U.S. and around the world to do their research at the ELL.

"We would like to stay competitive with other countries who are now building labs very similar to the one we built," he says. "You might say our model is being copied by other labs around the world and we want to stay in the game."

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ENSURING RELIABLE DATA

THE NEED FOR TOUGHER CONTROLS AS REGULATORS HOLD LABS TO EVER HIGHER STANDARDS

By Darren Barrington-Light

It's very difficult for patients and consumers to determine whether their medicines are safe to use and will work as intended. At the end of the day, it comes down to trust—trust in the manufacturer's production and quality control procedures, and in the decisions they have made to enable the batch to be released to the market.

As a result, the reliability of the data that underpins these decisions has long been of interest to pharmaceutical regulators. However, as pharmaceutical development, manufacturing, and supply chains have become more global and complex, regulatory authorities around the world are putting an increased focus on the completeness, consistency, and accuracy of this data throughout its life cycle.

Recent guidance released by the UK Medicines and Healthcare Products Regulatory Agency and the World Health Organization (WHO), as well as draft guidance released by the US Food and Drug Administration (FDA), have all put increased focus on data integrity.

Defining data integrity

But what does this term actually mean? While somewhat open to interpretation, the WHO and the FDA point to five key principles:

- Attributable: Who recorded the measurement or performed the experiment? And if changes were made, who did it, when did they do it, and why?
- Legible: Will the data still be legible 20 or 30 years into the future? Data must be permanently archived and readable in perpetuity—not just for the duration of the project.
- Contemporaneous: Was the data recorded at the time of measurement? Data collection should be supported by date and time stamps, leaving no room for ambiguity.
- Original: Is the record an original or approved copy? Even if a paper printout is transcribed into electronic format, the original copy must be retained.
- Accurate: Does the record reflect what was actually measured? Workflows should be designed to eliminate any potential for data to be changed from its true value.

> "Some of the most common data integrity issues raised by inspectors relate to the way in which electronic data is managed and stored."

With an increased focus on these areas, inspectors are looking for any weaknesses in laboratory workflows that may suggest that the environment in which data is collected, managed, and stored is uncontrolled. For pharmaceutical companies, this means being able to prove that results are an accurate reflection of what was measured, according to agreed-upon procedures, and demonstrate that robust control measures are in place to prevent any kind of loss in the integrity of this information.

The majority of chromatography laboratories have made the switch from paper-based systems to electronic processes. But although electronic data can be more secure, harder to modify, and easier to trace, it's only as good as the digital tools used to manage it. As a result, the most up-to-date chromatography laboratories are turning to integrated informatics platforms, based on a chromatography data system (CDS) and laboratory

information management system (LIMS), to ensure that they are working to the highest standards of data custodianship—and can easily demonstrate this to inspectors.

Transparency and traceability

Some of the most common data integrity issues raised by inspectors relate to the way in which electronic data is managed and stored. Here, ineffective internal procedures and inadequate informatics solutions are often to blame.

Earlier this year, the FDA issued a warning letter to an Italian pharmaceutical manufacturer for recording out-of-specification (OOS) data in an uncontrolled "preliminary" spreadsheet, while the laboratory's official reports indicated the products had successfully passed QC testing. [1] Despite the manufacturer's claim that a second analyst had retested the OOS samples to obtain the reported results, the regulator could find no documentation or audit trail to support this.

Such incidents highlight the need for robust workflow traceability in the chromatography lab. Thankfully, though, CDS and LIMS platforms offer a convenient solution. Most CDS packages not only securely archive the chromatograms, method parameters, and sequence data associated with a particular run but also all the user interactions made within the software. As a result, every processing event can be documented in the LIMS, along with the identity of the individual who performed it, ensuring complete transparency throughout the entire analytical workflow.

Advanced CDS platforms have the ability to version data sets, allowing users—and their supervisors—to compare changes made during processing. The software can even separate audit trails relevant to Good Manufacturing Practice so that lab managers can easily recall those necessary for review.

These comprehensive audit trails and fully searchable workflows can help limit the ability of analysts to perform "off the record" analyses and store data in "unofficial" worksheets. A search for sequences involving just a few injections or those that have been interrupted or aborted, for example, can quickly reveal actions that can subsequently be used by supervisors to further investigate unusual analysis workflows.

Consistent data analysis

When analyzing the purity of pharmaceutical products, standard operating procedures (SOPs) must be in place—and adhered to—in order to ensure reliable data, and this data must be underpinned by robust and reproducible peak detection and integration. Yet, inconsistent or incomplete data processing is a concern frequently cited by regulators.

Last year, a firm in the Czech Republic was sent an FDA warning letter highlighting serious deficiencies in the methods used by the manufacturer to assess the purity of drug products. [2] Inspectors found inconsistencies in the manual integrations of peaks in chromatograms, as well as peaks that hadn't been integrated at all. As a result, the manufacturer was required to review its existing procedures and implement suitable controls.

In an ideal world, all peak detection and integration would be handled by the CDS, but of course this can sometimes be challenging, with baseline noise, rider peaks, and other unresolved peaks adding a significant amount of complexity to the task of data analysis. Using sophisticated peak identification and integration algorithms, modern CDS platforms are helping deliver accurate and reproducible results with the minimum amount of analyst intervention, reducing or even removing the need for manual adjustments. Furthermore, intelligent run-control features built into the latest CDS solutions enable OOS injections to be automatically rerun according to defined method optimization protocols, helping analysts obtain high-quality chromatograms that can be more easily analyzed, automatically delivering more right-the-first-time analyses.

However, even with the most up-to-date informatics solutions, some user-defined integration may still be required. To help ensure that a consistent approach to workflow integration is adopted throughout the team, many chromatography laboratories are turning to enterprise-level CDS solutions, which provide smart graphical integration tools to aid the analyst in selecting appropriate parameters, and can easily identify injections that have been subject to manual interaction. With these chromatograms clearly marked, lab managers are much better placed to assess whether manual integration is being used according to the lab's SOPs.

Open and honest analysis

Other data integrity issues relate to not recording data at the time that it's collected, or not keeping original records. In one recent case, the FDA issued a warning letter to a manufacturer in India for data integrity breaches that included writing weight values on pieces of paper before transcribing them onto analytical worksheets and destroying the original copies.[3] Another violation occurred within the packaging area, with an operator recording product quantities before the batch had even been weighed.

Leaving a gap between the point at which data is measured and when it is entered into a system leaves data open to honest errors—or worse still, deliberate manipulation. While it may seem unnecessary and even a little inconvenient to retain original paper copies, these documents are the evidence to support the authenticity of the measurement.

Integrated informatics solutions supported by LIMS and CDS can record data as it happens, leaving little room for human oversight and non-compliant behavior. The latest LIMS platforms, such as Thermo Scientific SampleManager software, are capable of recording measurements directly from the instrument, such as a weight from a balance, eliminating paper copies and human error. And be-

cause all data collected, as well as any modifications that are made to the record, are recorded with user, time, and date stamps by the software, there is no room for doubt about the integrity of the data.

Furthermore, with a scientific data management system (SDMS) integrated into the LIMS, CDS and instrument data can be automatically archived and linked to results, ensuring data integrity across the laboratory and delivering the ability to demonstrate a very high level of data protection.

Part of the solution

Of course, robust data integrity controls will never be limited to the use of laboratory informatics software. For example, the requirement for adherence to written policies that hold individuals accountable for actions initiated under their electronic signatures, according to Title 21 of the Code of Federal Regulations Part 11, highlights the importance of staff training and the need for individuals to have a firm understanding of their responsibilities.

However, with regulators continuing to hold the industry to higher and higher standards, the leading pharmaceutical companies want to be better prepared than their competition. As part of their wider data integrity strategies, the most up-to-date chromatography laboratories are adopting integrated CDS and LIMS platforms to achieve the highest levels of data custodianship. Because when patient safety and consumer trust is at stake, the risks aren't worth taking.

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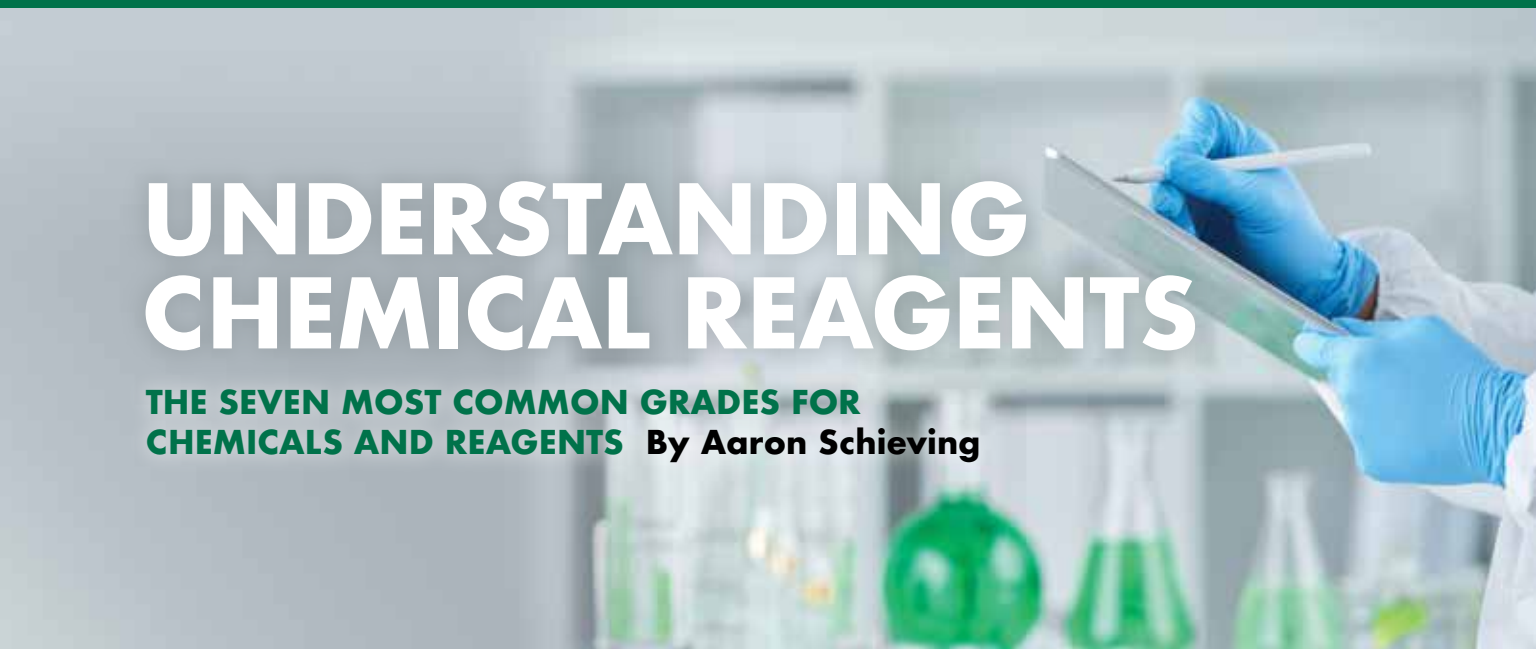

UNDERSTANDING CHEMICAL REAGENTS

THE SEVEN MOST COMMON GRADES FOR CHEMICALS AND REAGENTS

By Aaron Schieving

Chemicals and reagents play a critical role in the manufacturing and testing of pharmaceutical products, medical devices, biologics, cell- and tissue-based products, and many other healthcare-related solutions. Laboratories and researchers who use chemicals and reagents trust that their manufacturers have properly identified the grades of each chemical and ensured that the chemicals have met all regulatory and compliance standards for their intended use. It is imperative that everyone in the custody supply chain know and understand the different grades of chemicals and their uses, which are explained in this article.

When making a solution, the manufacturer must first decide what degree of chemical purity is needed based on the intended use. The following list describes the seven most common grades for chemicals and reagents, from highest to lowest grade/purity:

1. **ACS grade** meets or exceeds purity standards set by the American Chemical Society (ACS). This grade is acceptable for food, drug, or medicinal use and can be used for ACS applications or for general procedures that require stringent quality specifications and a purity of ≥95%.
2. **Reagent grade** is generally equal to ACS grade (≥95%) and is acceptable for food, drug, or medicinal use and is suitable for use in many laboratory and analytical applications.
3. **USP grade** meets or exceeds requirements of the United States Pharmacopeia (USP). This grade is acceptable for food, drug, or medicinal use. It is also used for most laboratory purposes, but the USP being followed should always be reviewed prior to beginning to ensure the grade is appropriate for that methodology.
4. **NF grade** meets or exceeds requirements of the National Formulary (NF). The USP and the NF (USP–NF) jointly publish a book of public pharmacopeial standards for chemical and biological drug substances, dosage forms, compounded preparations, excipients, medical devices, and dietary supplements. The listings here should be reviewed to determine which would be considered equivalent grades.
5. **Laboratory grade** is the most popular grade for use in educational applications, but its exact levels of impurities are unknown. While excellent for teaching and training, it is not pure enough to be offered for food, drug, or medicinal use of any kind.

> "When making a solution, the manufacturer must first decide what degree of chemical purity is needed based on the intended use."

6. **Purified grade**, also called pure or practical grade, meets no official standard; it is not pure enough to be offered for food, drug, or medicinal use of any kind.
7. **Technical grade** is used for commercial and industrial purposes; however, like many others, it is not pure enough to be offered for food, drug, or medicinal use of any kind.

ACS, Reagent, and USP-NF grades are typically equivalent and interchangeable but, even so, appropriateness should always be confirmed before application. This can be done by reviewing the applicable regulatory requirements.

Lab, purified, and technical grades have their own uses. For example, lab-grade chemicals, because of their low cost and good chemical purity, are used widely in educational applications, such as teaching laboratories at both the secondary school and college levels; however, lab-grade chemicals would not be appropriate for use in the quality control laboratory of a pharmaceutical or medical device manufacturer. ACS-, USP-, or reagent-grade chemicals should be applied in this setting, because they have fewer impurities that could ultimately impact patients taking the drugs made with those chemicals.

"ACS, Reagent, and USP-NF grades are typically equivalent and interchangeable."

With seven different and inequivalent types of chemical purity grades, it is crucial to understand how they can impact products. Using a lower-purity grade than a product's intended use requires could be a costly mistake. Similarly, using a higher-purity grade when not required could result in unnecessary costs. Add in the increased regulatory scrutiny and it becomes even more important to have a complete understanding of the components that your process requires.

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MAKING CONNECTIONS

FOR TODAY'S SCIENTIST, PROFESSIONAL NETWORKING MATTERS

by Sara Goudarzi

To many professionals, networking—the idea of finding acquaintances for mutual professional gain—is a cringe-worthy concept. Often, the thought conjures up images of awkward introductions and uncomfortable silences. Therefore, many shy away from events that encourage making such connections. Despite this, most everybody understands there are a variety of benefits to knowing other professionals in their fields—especially in the sciences, where collaborations could be key to further advancing a field.

For Kelly McKinnon, a PhD candidate and researcher at the Woodruff Lab at Northwestern University, the importance of networking was apparent early on in her career.

One of the first projects she was involved with at Northwestern was developing Evatar—the laboratory group's ex vivo female reproductive tract in a microfluidic system. This was something that had never been done before and required collaborations between multiple departments and institutions to succeed. Evatar consists of 3-D tissue models of the ovaries, fallopian tubes, uterus, cervix, and liver in a system that allows for communication between each tissue through circulating media. Programmable through a computer interface, it has pumps and channels to carry the nutrient media from culture to culture, similar to how our hearts and vessels do so in our bodies. Every one of the pieces of this system required a specialist in that field.

> "Often relationships built during smaller, local meetings can be very productive."

"Each 3-D tissue model was produced and validated by experts of that tissue independently before we ever put anything together," McKinnon explains. "We also had a team of engineers at both Northwestern and Draper Labs who worked on the actual system mechanics, flow rate, etc."

McKinnon and her advisors held weekly meetings with the entire group, a crucial requirement for engineering a system capable of supporting the physiological needs of these tissues.

The team went through many iterations, but it was the constant dialogue between the engineers, biologists, and subject experts that made the project a success. Together, they were eventually able to culture all five tissues for a 28-day hormone cycle, with the ovaries producing cycling levels of estrogen and progesterone, and each of the downstream tissues responding to ovarian hormones, like they would in the body.

"Taking on a project that was a little outside of Dr. [Teresa] Woodruff's expertise [ovarian biology and reproductive endocrinology] required that I collaborate and network from the very beginning," McKinnon says.

And she isn't alone in her need to work, and interact with, others. For many lab professionals, it's a necessity to be aware of, and involved with, experts in their fields and sometimes with those in other fields, as exemplified above.

For A. Christian Whelen, administrator at the State Laboratories Division of the Hawaii Department of Health, occupying a leadership position in state public health as a laboratory director means he needs to work with various internal and external stakeholders.

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"Internally, our laboratory supports multiple disease control and environmental quality programs," he says. "It's critical that the state laboratory director and the state epidemiologist are tightly coordinated when responding to public health diseases, such as Hawaii's 2015–2016 dengue outbreak or [the] current mumps outbreak."

Externally, Whelen routinely interacts with public health labs in other jurisdictions, clinical laboratories for reportable disease submission of specimens or isolates and personnel licensing, community colleges and universities for strengthening lab science education and applied research, environmental laboratory certifications, first responders for biological and chemical incident response, and community and political leaders to explain the importance of their public health laboratories in maintaining Hawaii as a favorable place to live, work, and play.

Networking routes

Traditionally, lab professionals networked by belonging to professional associations and attending and presenting at association meetings. Conferences were yet another established opportunity for meeting others in the field.

"For me, personally, since my work is so interdisciplinary, I go to both reproductive science meetings and cell biology meetings to present my work," McKinnon says. "This allows me to bring reproductive science to a field that may not necessarily be thinking about it, while also getting feedback that I wouldn't be able to get at a reproductive science meeting."

Though these larger events are important for national networking, Whelen cautions that "folks shouldn't disregard local chapters and regional meetings."

"Often relationships built during these smaller, local meetings can be very productive," he adds.

Through these time-tested methods, lab professionals are sure to be able to extend their networks. However, with the advent of technological networking, more avenues are now available for managers to get to know, and keep in touch with, their peers.

"Technology has revolutionized the way we communicate with each other in the modern world," says Chuba Oyolu, founding scientist at Counsyl Inc., a health technology company that specializes in DNA screening (South San Francisco, CA). "Prior to the advent of tools like Facebook and LinkedIn, the onus was on the individual to email or physically visit the institutions that they were interested in joining and sell themselves to potential employers. Thanks to the professional online profiles that many of us now have, it is not uncommon for employers to initiate contact with potential candidates for open positions within the organization."

"In short, having an online social media profile has drastically simplified the process of being found and approached for jobs for which you may not have even known existed but for which you'd be a perfect fit," Oyolu adds.

Approaching other professionals

Despite the avenue of making contact—be it in person, on the phone, or electronically—professionals still have to approach each other in order to make contacts. How one goes about this depends on the individual and the circumstances because every person has a unique disposition.

"It can definitely be difficult, especially if you're naturally an introvert, as I am," McKinnon says. Even so, she has her techniques to get over the difficulty of interacting with other scientists.

"What helps me at conferences or networking events is just jumping straight into the science," she says. "If the normal small talk feels unnatural, talk about what you're confident about—your research. You'd be surprised by how even the most socially awkward people—I'm looking at you, engineers—come out of their shells and shine when talking about their work."

As far as McKinnon is concerned, if researchers are passionate about their work, it's easy for them to talk about their research.

"Be a good listener, and come up with an insightful question," she says. "One good question that shows you were really listening will be remembered more favorably than 15 minutes of small talk in most cases."

Though he cautions there is no single correct method on how one approaches another person, Oyolu agrees that asking questions is a good way to approach others. For him, walking up to people is the way to go.

"One thing I have noticed about people from all types of backgrounds is that they generally like to talk about themselves," he says. "If you can get someone talking by just asking them questions about their life and work while you attentively listen, you'll have no problem networking and making friends."

It's possible that being an introvert is a common trait among those in lab careers. Whelen believes many gravitate toward laboratory sciences specifically to make scientific contributions while avoiding the limelight. All the same, it's a comfort zone that, like others, he knows he needs to step out of once in a while.

"I try to learn as much about organizations and colleagues as I can before interactions," he says. "That helps me find common ground, which facilitates conversation[s] and relationship building."

Another strategy McKinnon employs at conferences is to sit at a different table for each meal, rather than sitting with the people she already knows. By making a point to sit with new people at each meal, she is able to expand her network, hear about different research, and perhaps make some new friends.

"The first few minutes might be awkward, but I've met so many people and made so many connections by just following this simple strategy," McKinnon says. She also suggests third-party introductions, either at an event or via email. "People see you in a different light if someone they know personally brings you to their attention."

A necessity of professional life

No matter the strategy, nor the feeling toward it, networking allows people to grow both individually and toward an overarching scientific goal, because they need to be able to exchange ideas and processes to learn and advance.

"I've had the good fortune of working in multiple fields throughout my life, and the pattern is always the same: Regardless of how smart, talented, or capable you are, you will need people to help you reach your highest potential," Oyolu says. "You will typically learn from the folks around you at a much faster pace than you could learn on your own. You'll learn everything from what to do in order to be successful to what to avoid doing to keep from sabotaging yourself and your career."

And to have the cooperation and contributions of their peers, lab professionals need to be out there, visible to colleagues—whether that's in real life or virtually.

"They can't help me and I can't help them if I remain invisible," Whelen says. "Equally important is networking with other public health laboratories and professionals. If I encounter an unfamiliar situation or problem, there's a good chance that one of my colleagues has experiences to share."

And sometimes, visibility comes in handy during the most unexpected times, even when one is not looking to network. When in South Dakota for his high school class reunion last summer, Whelen dropped by to see his counterpart, the director of the South Dakota Public Health Laboratory.

It turned out Timothy Southern was very interested in how Hawaii works with the other U.S.-affiliated Pacific island jurisdictions. He described to Whelen difficulties with public health laboratory outreach to Native American nations in South Dakota, which struggle with access to healthcare, including timely laboratory diagnostic testing.

"We decided to approach the Centers for Disease Control Epidemiology and Laboratory Capacity program managers and propose a lab-to-lab mentoring relationship to investigate the potential for applying strategies that have worked in the Pacific to Native American nations in South Dakota," Southern says. "That was unexpected."

This unanticipated partnership is another example that networking, not just in public health laboratories, but in all labs, is critical to ensuring that preparedness and response capabilities are available when necessary. "No lab can do everything, but as a community of laboratories—there's nothing we can't do," Whelen says.

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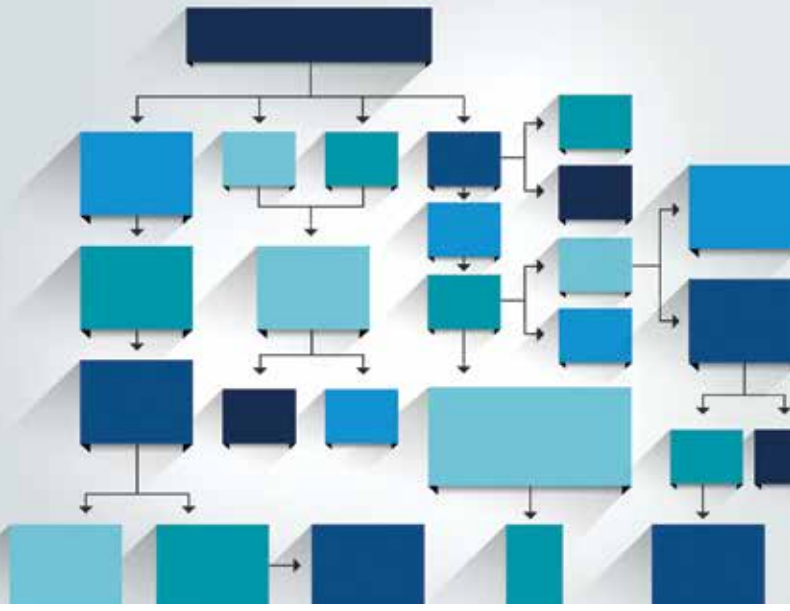
FIGURING OUT FLOW

VARIOUS TOOLS AND TECHNIQUES HELP SCIENTISTS CUSTOMIZE THEIR WORKFLOWS by Mike May, PhD



A lab's efficiency revolves around workflow—how samples get prepared and data get collected, analyzed, and interpreted. An effective workflow even impacts the reproducibility of data in the lab, because the right system ensures that something gets done the same way every time. The tricky part is that most labs need some customizing of their workflow, something that fits just right with their research objectives and personnel.

The best approach to improving a lab's workflow comes from a variety of approaches, and some depend on the kind of lab. When asked for two top suggestions for improving the workflow in a small academic lab, Lisa Thomas—senior director, marketing, life science mass spectrometry at Thermo Fisher Scientific (Waltham, MA)—goes with quality control and designing a scalable process from the start.

▲ *An electronic lab notebook helps scientists keep processes and information organized, which improves a lab's workflow. (Image courtesy of sciNote.)*

For quality control, she says, "Implementing off-the-shelf certified calibration solutions in any method you develop and potentially plan to run routinely even in a research setting is just good laboratory practice." Calibrated solutions can save time and add accuracy in many technologies, such as liquid chromatography (LC) and mass spectrometry (MS). As an example, Thomas notes, "Thermo Scientific Pierce Calibration Solutions for mass spectrometry are ready-to-use liquid formulations that can quickly aid in calibrating our LC-MS instrumentation and help determine when something isn't right."

In addition to calibration standards, quality control involves many other elements. For instance, Thomas encourages scientists to use standards for sensitivity assessment, for determination of digestion efficiency, or as a control for sample analysis. These standards increase the odds of experimental success, and they can reduce variability compared with using some do-it-yourself approaches. "High purity, validated mobile phases, and acidic ion-pairing agents are essential for achieving effective and reproducible liquid chromatography separation of peptides for electrospray ionization MS," Thomas explains.

Seeking scalability

The complexity of the research environment—not just planning and running experiments but also finding ways to fund them—makes it easy to get tunnel vision, focusing only on the job at hand. Given that funds come with limits, keeping workflows running as smoothly as possible requires some thinking ahead.

If a workflow fits only a lab's current needs and provides no room for growth, any need to increase throughput or handle more samples could require going back to the drawing board, reworking the entire process from scratch. For example, a

method could be able to increase in scale if it includes some automation from the start. Then, if a lab needs to run more samples, the automation can be adjusted without changing the entire process.

Tools for factoring in the future already exist, and the options keep increasing. "More vendors offer scalable solutions, like the Transcend II HPLC System, where you can incrementally add up to four channels as demand rises," Thomas points out. "Or look for innovations that enable plug-and-play modular configurations to a single mainframe, like the Trace Series gas chromatograph, which enables users to rapidly change or add injection and detector options to suit their testing needs or simply keep their systems online."

Sometimes scientists just don't know what will do the most to improve a workflow. When possible, ask a vendor for a demonstration, especially with smaller devices. "For large instrumentation, looking to connected lab capabilities can be key," Thomas explains. "Our Thermo Fisher Connect enables labs to boost productivity with secure, remote access to data and instruments."

A family tradition

Some solutions to chromatography start at home. In an Apple-like beginning, Phillip James started a chromatography company in a back room of his house in 1994, and he named it Cambridge Scientific Instruments. The first products were chromatography accessories, including an electronic programmable pressure controller for gas chromatography (GC) and a vacuum degasser for LC. Today, his company is known as Ellutia (Ely, UK), and it makes complete GC platforms, including the 200 Series GC. The founder's son and marketing director at Ellutia, Andrew James, says, "We try to fill a niche, producing custom solutions and systems for people to solve problems that other manufacturers are not willing to solve."

For custom or off-the-shelf solutions, GC can create various workflow obstacles. "As GC manufacturers," says James, "we see several stages of GC analysis, all of which have potential bottlenecks." Those bottlenecks start at the beginning, with sample preparation. "Getting samples to the stage where they can be introduced to GC can be a long-winded process and very manual," James explains. This stage involves mixing chemicals, processing the sample, and so on—all of which can slow down a workflow or make it less repeatable. In an ideal scenario, a user places the

raw sample into a vial, and then an automated system completes the sample prep, introduces the sample to the GC, completes the analysis, and produces the report, all with the press of a single button, but that capability remains futuristic.

The GC platform matters, too, in workflow. GC comes in three main forms: conventional GC, the traditional column in an oven, which runs in from 30 minutes to a couple of hours; fast GC, which uses an oven with shorter and narrower columns to reduce the analysis time, but at the cost of sample capacity and detection limits; and ultrafast GC, which uses rapid direct heating of a column with electric current, reducing the run time to five or six minutes. "This is great for method development, where you try something, change something, and try it again," James explains, "because you can do it faster and easier." Later in 2017, Ellutia will release a GC platform that can do all three techniques.

After running a GC, data become the next potential bottleneck. Depending on a lab's needs, this stage can range from software that comes with a GC platform to implementation of a full laboratory information management system (LIMS), which can automate many steps in the process.

Beyond helping customers address a range of slow spots in a GC process, Ellutia even designs custom solutions. "This covers quite a broad range," James says, "from a customer looking at permeation of rubber gloves to a nuclear power station monitoring reactor gases to a portable ultrafast GC to do on-site analysis at gas stations." In thinking about tackling such diverse problems, James says, "It's fun and interesting because you get your eyes opened to different industries and things you might never have dreamed of when we first started this company."

Keep it organized

For any workflow, organization adds efficiency. "To develop efficient workflows, organizations need flexible software solutions that can adapt to the way labs are performing their work," says Klemen Zupancic, CEO at sciNote (Middleton, WI). The solution needs to be flexible enough to handle a range of scales and lab processes.

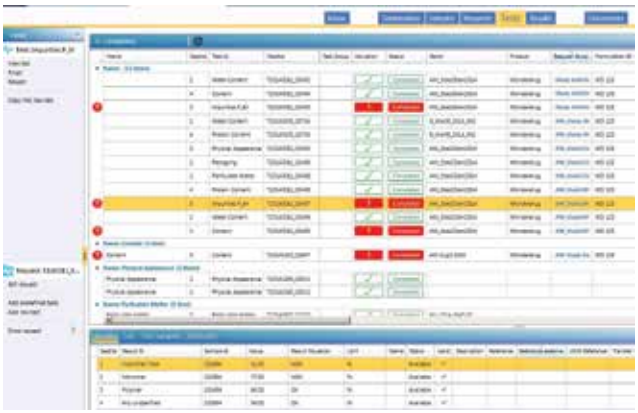
An organizational tool must also communicate with software on various platforms. "The best solution will not reside in one piece of software but rather a network of systems," Zupancic says. So his company developed sciNote—a free electronic lab notebook—as modular, open-source software. "We encourage interoperability between different software solutions and lab instruments," he says.

Other tools for connecting technologies also exist. As Garrett Mullen, program product owner for informatics at Waters (Milford, MA), says, "There are technologies available on the market that provide for the interfacing of simple devices, like balances and pH meters, that can automatically capture and store data, ensuring correct digits and units of measure are captured."

Other digital tools help scientists manage automated workflows, and these tools range from simple to complex. "An example of a simple technology is valuation tools on a digital form that compare actual results to desired or target results at time of capture," says Mullen. "These tools can be as simple as a green check or a red X that indicates whether an expected result or value is in or out of specification."

Where to start

To improve any workflow, it helps to know where to start. A good place is the most repetitive process in a lab. "Measure the process from beginning to end and record all of the manual data entry and recording steps, looking at



▲ *Some tools make it easier to manage automated workflows, such as this example that includes a 'green check' or a 'red x' to indicate when a result is in or out of specification. (Image courtesy of Waters.)*

each review step as well as the number of sign-offs required," Mullen suggests. "Identify which tasks can be automated or eliminated and which are most frequently a source of error."

With a key bottleneck identified, think about ways to automate it. "Not all processes can be automated, but do not be discouraged," Mullen says. "Work with the ones that can, and you will have more time available to improve those processes that cannot be automated."

It's not just the mechanical work but also keeping track of information that matter. That means keeping together information from a workflow. "For example, scientists often need to account for which samples were included in a specific part of the experiment and which results they generated," Zupancic explains. "In addition, they should also track which instrument was used to generate their raw data as well as who analyzed and confirmed the results, and when."

"The best solution will not reside in one piece of software but rather a network of systems."

So, getting the most from a specific workflow requires analyzing it. After that, a scientist must imagine an improvement, find the technology to make it happen, and then test the outcome.

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MODELING AND SIMULATION

EMPLOYING VIRTUAL PATIENTS TO ADVANCE DRUG DEVELOPMENT

by Ellen Leinfuss

Computer modeling and simulation, also known as *in silico* modeling, has become a vital part of the drug development process. It has progressed beyond being a scientific nicety and is now considered a regulatory necessity.

Widely adopted by biopharmaceutical companies and regulatory agencies worldwide, it is used throughout the research and development (R&D) process from discovery through the preclinical and clinical phases, and ultimately to evaluate new drugs and biologic applications. It is also employed to inform new drug labels, including potential drug-drug interactions, dosing regimens, and data about new populations, once products are approved to go to market.

> "Replacing drug-drug interaction clinical studies with virtual ones can shave years off the drug development timeline."

Modeling and simulation can help guide critical decisions around dosing and toxicity, efficacy and mechanism of action, clinical trial design and cohort selection, and commercial probability of success as compared with existing therapies or others in development.

Regulators weigh in

US Food and Drug Administration (FDA) Commissioner Scott Gottlieb, MD, announced on July 7, 2017, that under the 21st Century Cures Act, the agency will be "investing in, and will be expanding on…the use of *in silico* tools in clinical trials for improving drug development and making regulation more efficient."[1]

"Modeling and simulation play a critical role in organizing diverse data sets and exploring alternate study designs. This enables safe and effective new therapeutics to advance more efficiently through the different stages of clinical trials,"[1] said Dr. Gottlieb.

"FDA's Center for Drug Evaluation and Research is currently using modeling and simulation to predict clinical outcomes, inform clinical trial designs, support evidence of effectiveness, optimize dosing, predict product safety, and evaluate potential adverse event mechanisms,"[1] he added.

This technology is also being employed by the European Medicines Agency, the Japanese Pharmaceuticals and Medical Devices Agency, and other global regulatory agencies to evaluate new drug submissions.

Helping vulnerable patient populations

One of modeling and simulation's greatest strengths is its ability to determine the most appropriate drug dose for vulnerable populations—such as pediatric patients, pregnant women, oncology patients, those with rare diseases, and patients with either impaired organ function or a compromised immune system—on which drugs cannot be tested.

There are numerous practical, ethical, and legal reasons why pregnant women and pediatric patients rarely participate in clinical trials. As a result, clinicians do not have access to a recommended drug dose to prescribe for them. In many cases, they must extrapolate from the existing adult dose and use their best clinical judgement to decide on the most appropriate dose.

The situation is especially complicated with pregnant women because clinicians have to consider the potential impact of the drug on both the mother and the fetus. They

also have to factor in the changes that occur to the pregnant woman's physiology and absorption, distribution, metabolism, and excretion, which vary by trimester. These changes can result in the level of active drug in a pregnant woman's body being significantly lower or higher than usual, potentially producing a subtherapeutic dose or a toxic one.

Establishing recommended drug doses for pregnant women is still a largely unmet medical need. The Centers for Disease Control and Prevention reports that less than 10 percent of medications approved by the FDA since 1980 have sufficient information to determine their risk for birth defects.[2] Furthermore, most pregnant women are prescribed one drug during their pregnancy, and half of them take four or more.[3] They could be drugs to treat a preexisting illness, a newly acquired bacterial or viral infection, or a pregnancy-related condition.

It would also not be possible to investigate in clinical trials all the drug-drug and drug-food interactions that could potentially occur in patients with comorbidities, or patients with complex diseases such as cancer or HIV infection, who receive polypharmacy.

In addition, it can be difficult to perform clinical trials for rare diseases, including many types of cancer, due to the small number of patients and the fact that they are often geographically dispersed. It can be especially difficult to identify patients who have not received alternative investigational medications. The issue around patient identification was recently highlighted in the New York Times, in an article titled "A Cancer Conundrum: Too Many Trials, Too Few Patients."[4] Modeling and simulation can be leveraged to separate the wheat from the chaff with regard to R&D investment.

Testing drugs in virtual patients

Modeling and simulation has proven to be an effective solution when it is impractical to conduct specific clinical trials. It allows "what if" questions—such as evaluating potential drug-drug or drug-food interactions or the impact of a change in clinical trial design—to be answered in virtual patients, while minimizing the use of human subjects. It also maximizes the predictive value of the limited clinical trial data available.

Pharmacokinetic/pharmacodynamic (PK/PD) modeling has essentially become a required element in the study and approval of most novel drugs. In the preclinical phase, modeling and simulation is used to support first-in-human dose justification, translate from animal to human data for safety and efficacy, and assess cardiac risk failure. From phase 1 through proof of concept (POC), it is used to model the time course of the disease, the compound effect, and the effect of different patient variables. It is used to support strategies to evaluate proof of mechanism and optimize clinical pharmacology requirements including drug-drug and drug-food interactions. Assuming a compound has progressed through POC, modeling and simulation is leveraged to evaluate population PK and exposure-response design, optimize alternative formulations, perform comparative effectiveness analysis, and provide a quantitative basis for final dose and dosing regimen.

> "Pharmaceutical companies are increasingly conducting virtual clinical trials in parallel with real-world ones."

Proprietary whole-body modeling and simulation technology can demonstrate how small-molecule and biologic drugs will behave in the human body (PK) and how the body will respond to them (PD) based on laboratory-derived data. A population-based simulator also features unique genetic, physiologic, and epidemiologic databases that allow it to simulate virtual populations with different demographics and ethnicities.

This approach can also be used to conduct virtual bioequivalence (BE) studies. For example, the multiphase, multilayer skin model permits the virtual BE assessment of two drug formulations such as cream and gel, or the same formulation type with a different pH, viscosity, or base. These virtual BE studies also save sponsors both time and money.

To assist researchers in determining the most appropriate drug doses for pregnant women, the simulator includes a pregnancy model, which simulates drug exposure not only in the patient but also in her fetus and placenta.

This model reflects the physiological and biochemical changes that occur in the mother's body during each trimester. Therefore, researchers can determine how systemic drug exposure would vary at different stages of the pregnancy, allowing the dosage to be adjusted accordingly.

Enabling virtual trials to inform real-world ones

Pharmaceutical companies are increasingly conducting virtual clinical trials in parallel with real-world ones, conducting the virtual trial first and allowing knowledge gained there to inform the real trial. This parallel development strategy can similarly be applied in the prediscovery, discovery, and preclinical research stages.

This method resembles a series of concentric circles in which information gathered from the virtual phase 1 trial is incorporated into the design for the real phase 1 trial. Then data generated from the real phase 1 trial is used to inform the virtual phase 2 trial, and so on. This paradigm does not have to follow the traditional linearity of drug development; for example, data from post-marketing information can be used to inform new drug discovery and translational programs.

This is a particularly powerful approach because testing drugs in virtual patients will always be less risky than testing in real ones. Of equal importance is the increased speed and reduced cost that the use of virtual trials affords. In most cases, modeling and simulation facilitates the simplification of trials, at lower cost. And in some cases, *in vivo* trials can be replaced by *in silico* ones.

Making precision dosing a reality

Modeling and simulation is also starting to be used to determine the best drug dose for individual patients in clinical care.

This approach, which factors a patient's unique genetic makeup and pertinent biomarkers into the model, is currently being employed to treat patients with complex cases in the hospital research environment in the US, UK, Europe, and Australia. These cases include patients who have undergone bariatric surgery, have received a cell or organ transplant, or suffer from a psychiatric disorder, complex infection, or rare genetic disease.

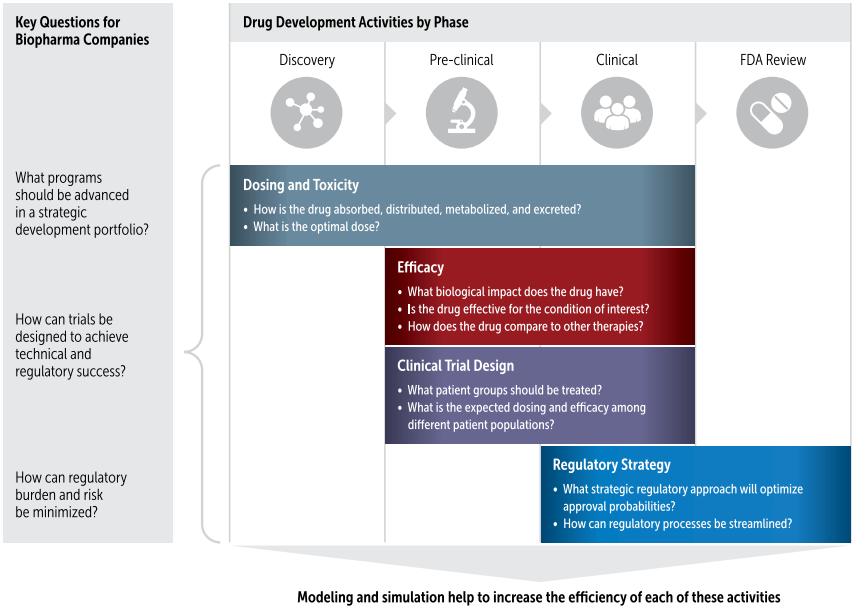
The goal of this form of precision dosing is to provide each patient with the right drug dose, which maximizes therapeutic benefit while reducing risk.

Conclusions

Modeling and simulation has an important role to play throughout the drug discovery and development continuum, improving decision making and removing some of the risk from the process. It helps to ensure that the correct go/no-go decisions are made regarding new drug candidates, minimizing phase 2 attrition and making sure that chosen study drugs have the intended therapeutic benefit with fewer adverse effects.

During the next few years, as clinicians become increasingly comfortable employing modeling and simulation and adopting its recommendations, it is expected that precision dosing will enter mainstream healthcare.

Looking a little further ahead, it is predicted that every patient will have a personal avatar on which every health and wellness intervention can be tested before they receive it. Modeling and simulation promises researchers and clinicians the ability to deliver a truly personal healthcare experience to patients.



▲ *Modeling and simulation, along with regulatory science solutions, provide insights into key questions faced during drug development.*

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HAZARDOUS OR NOT?

HOW TO DETERMINE AND MANAGE HAZARDOUS CHEMICAL WASTE IN YOUR LAB

by Vince McLeod

Improperly managed hazardous wastes pose serious threats to human health and the environment. Whether you work in academic, research, development, or production labs, the diverse processes can present complex challenges, especially when it comes to proper waste handling.

And, should you be visited by local, state, and/or federal inspectors, you will quickly realize the importance of knowing all your waste streams and understanding the myriad regulations on handling and management. One of the most common transgressions uncovered by inspectors is a failure to fully determine the hazardous characteristics of all wastes.

This month, the Safety Guys present an overview of hazardous waste management. We focus on laboratory chemical wastes, because these are the main offenders when it comes to waste streams in research or production facilities.

Proper management of chemical waste is not only important for the environment and human health, but also for safety and economic concerns. Serious fines and penalties are possible if wastes are not handled according to regulations.

Understand the basic regulatory framework

The main governing body when it comes to hazardous waste is the Environmental Protection Agency (EPA), which developed a cradle-to-grave process first promulgated in 1976.[1] The process regulates hazardous waste from the time it is created to while it is transported, treated, or stored to the time of its final disposal. This regulation is known as the Resource Conservation and Recovery Act (RCRA).

Although the EPA regulation establishes the baseline, we must emphasize that some states and local jurisdictions have waste or chemical management requirements that go beyond the EPA. Therefore, it is critical to check with state and local entities regarding any additional requirements.

Characterize all wastes and identify the hazardous wastes

The burden is on the generator, i.e., the creator of the waste, to characterize all wastes produced by the lab or facility and identify those that are hazardous. RCRA defines which wastes are hazardous, i.e., managed cradle to grave. The details are contained in the Code of Federal Regulations, Title 40, Protection of the Environment, parts 260 to 265.[2]

Specific lists of hazardous chemicals that when disposed of become hazardous chemical wastes are given a waste code. For the average laboratory, a waste is considered hazardous if any components are on one of two lists of chemicals (P-list for acutely hazardous or U-list for general toxic chemicals).

The U-list covers discarded chemical products, off-specification chemicals, container residues, and spill residues that have been identified as toxic wastes and receive a corresponding U-code. The P-list refers to a special sublist of compounds identified as acutely toxic and subject to smaller quantity exclusions. These lists are found in 40 CFR 261.33.

In addition, there are smaller lists for chemicals from nonspecific sources, mixtures of spent solvents, wastewater sludges, and distillation bottoms, which fall under the F-codes (found in 40 CFR 261.31). Wastes from specific procedures such as wastewater treatment sludges and distillation wastes from certain chemical production processes receive a K-code (found in 40 CFR 261.32).

Evaluating waste characteristics

But, what if your lab generates a waste stream and it does not contain any U-listed or P-listed material, and does not fall into one of the F- or K-listed categories? How do you make a determination of whether the waste

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- Assign the team and make it lean
- Seek input across the company
- Plan for measures to mitigate risk
- Expect the unexpected with a back-up plan

Step 2 Define

- Consider the logistics: Decommissioning… Packing… Unpacking… Transporting… Hazmat Handling… Recommissioning… IT Connections… Temperature Control… Global Regulatory Compliance…

Step 3 Communicate

- Determine who needs to be in-the-know. From lab managers to business leaders and supply vendors to facility managers and general company employees – **an internal and external communications plan is crucial to the success of a laboratory relocation**

Keep an eye on lead time – determine what needs to be planned for in advance like "Goods in Transit" insurance, regulatory documents that need to be processed, time-sensitive and temperature controlled projects.

Step 4 Contingency Plan

- Plan for multiple scenarios even the worst case scenario so your team is prepared with a contingency plan
- Know your partners, providers and outside vendors and their policies and if there is room for flexibility

Step 5 Partner

- Choose a single solution provider with proven experience

The ideal partner provides end-to-end turnkey service, guiding you through the early planning stages to full operation of the lab in your new location. This would be managed under one purchase order, as one project management agreement, with one point of contact — eliminating fragmentation of multiple service providers.

Contingency planning should include a RAID — Risks, Assumptions, Issues, and Dependencies — or Risk Register. Created at the start of the project and updated daily, the RAID lists any potential risk or issues, which are "opened" if they occur and tracked throughout the project until resolved.

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is hazardous or not? Very simply. You must determine whether it meets one of the hazardous characteristics: ignitability, corrosivity, reactivity, or toxicity, as defined in 40 CFR 261.20.

All waste streams, including unconventional, temporary, or short-term wastes, need full characterization for proper disposal. As mentioned above, the four hazard characteristics are ignitability, corrosivity, reactivity, and toxicity. Testing is sometimes avoided with sufficient general knowledge, i.e., knowledge of the specific constituents used and the process by which the waste is generated. In most cases, however, representative samples are collected and tested to make the determination.

Ignitable wastes are given the code D001 and exhibit any of the following properties:

- A liquid that has a flash point less than 60°C (140°F), determined by the Pensky–Martens Closed Cup Tester or the Setaflash Closed Cup Tester;
- A nonliquid that is capable of causing fire through friction, adsorption of moisture, or spontaneous chemical changes;
- An ignitable compressed gas as defined in 49 CFR 173.300; or
- An oxidizer as defined in 49 CFR 173.151.

Corrosive wastes are given the code D002 and exhibit any of the following properties:

- Aqueous liquid with a pH less than 2 or greater than 12.5; or
- A liquid that corrodes steel at a rate greater than ¼ inch (6.35mm) per year at a test temperature of 55°C (130°F).

Reactive wastes are given the code D003 and exhibit any of the following properties:

- Is normally unstable and undergoes violent change without detonating;
- Reacts violently with water;
- Forms potentially explosive mixtures with water;
- Generates toxic gases or vapors when mixed with water;
- Is a cyanide or sulfide containing waste that can generate toxic gases or vapors;
- Is capable of detonation or explosion if heated or subjected to a shock; or
- Is an explosive as defined in 49 CFR 173.

Toxic wastes are given a D-code if any of the toxic compounds listed in Table 1 of 40 CFR 261.24 are present, and equal to or above the respective limits as determined by the Toxicity Characteristic Leaching Procedure, known as TCLP. This is basically a water-extraction procedure for determining whether toxic compounds can leach out of the waste. TCLP is defined in Test Method 1311.[3]

In these cases, we encourage you to contact an experienced consultant to assist with sampling and testing waste to determine whether it has any hazardous characteristics. If the waste is not hazardous, then disposal locally via the sewer system or the general refuse collection

might prove an alternative. However, we caution you again to confirm with local providers and authorities to ensure all local codes and ordinances are followed.

Summary

To operate safely and to avoid potentially expensive regulatory fines, proper management of hazardous chemical waste is paramount. If you are new to handling laboratory wastes, this article should get you moving down the right path. If you are an experienced lab manager, then hopefully there is some useful information here to help you review your current operations.

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FRAGMENT-BASED METHODS FOR DRUG SCREENING

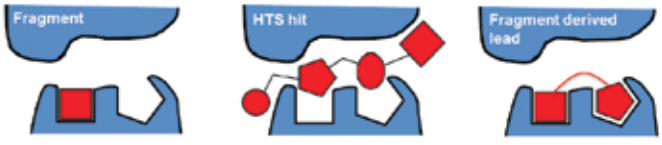
WITH FEWER SMALLER CHEMICALS, SCIENTISTS DEVELOP MORE-TARGETED MEDICINES

by Mike May, PhD

In the pharmaceutical industry, the "batting average" for taking a compound from discovery to a marketed therapy leaves a lot to be desired. Consequently, pharmaceutical scientists keep looking for new techniques. While these scientists are thinking big, something smaller may be needed—particularly when it comes to searching for new lead compounds to test as medicines.

A promising lead candidate should be specific and selective, targeting one site and only that site. That's not so easy to find, because many molecules cling to too many others, and bigger molecules have more potential binding regions. Instead of working with those big molecules, pharmaceutical scientists can work with fragments—smaller pieces of potential drugs. Fragment-based drug discovery (FBDD) is helping scientists screen for potential medicines in new ways.

With larger, traditional molecules, pharmaceutical scientists use high-throughput screening (HTS)—such as some spectroscopic readouts from an enzyme-based assay—on libraries of a million or more components in search of new drugs. With smaller chemical fragments, screening only a few thousand of them often turns up a molecule that inhibits the target, although probably weakly. That inhibitor can then be optimized—made into a bigger molecule—to attack that target more strongly.



▲ *Fragments can fit target sites more precisely (left) than larger molecules found in high-throughput screening (middle), and then a fragment can be built into an even more tightly binding lead candidate (right). (Image courtesy of Astex Pharmaceuticals.)*

The compounds in a fragment-based screening library are 150–200 Daltons, compared to 400–500 Daltons for an HTS library. "With the smaller compounds," says David Rees, chief scientific officer at Astex Pharmaceuticals (Cambridge, UK), "you can do a better job of screening all possible structures that might be available, because the total number of structures increases exponentially as molecular weight increases." With the fragments, there are fewer possible structures to test.

▲ *This fragment binds a protein's active site. (Image courtesy of Seth Cohen.)*

In a 2017 issue of the *Journal of Medicinal Chemistry*, David Bailey, director at IOTA Pharmaceuticals (Cambridge, UK), and his colleagues wrote: "The early-stage hits generated from fragment-based programs may have more favorable physicochemical properties compared [with] those resulting from high-throughput screening." The authors added that more than 30 compounds from FBDD are in clinical trials, and two—vemurafenib and venetoclax—are on the market.

The current use of FBDD is just a start. It provides a wide range of benefits that will likely drive this approach into more pharmaceutical science ahead. In fact, scientists are only just exploring some of the ways to apply this approach.

OPTIMIZING OPPORTUNITIES

"It's been suggested that the quality of interactions that fragments make with their target is potentially better than large, complex molecules," says Seth Cohen, professor of chemistry and biochemistry at the University of California, San Diego. Cohen is also a co-founder of Forge Therapeutics, a start-up company that utilizes FBDD for drug discovery.

In part, smaller molecules bind in a more idealized manner. A larger molecule has to accommodate multiple interactions at once, which makes for suboptimal contacts. "Fragments can make key interactions with the active site, so you can see how it fits and then elaborate on that while preserving that original interaction," Cohen explains. "You build your molecule piece by piece." In addition, fragments can deliver higher hit rates, especially for more difficult drug targets, Rees notes.

At Astex, scientists used FBDD to discover an inhibitor of two proteins involved in cell death, and this spurred the development of ASTX660—an Astex molecule that is "currently being evaluated in a Phase 1/2 study in patients with advanced solid tumors and lymphomas," Rees says.

"An increasing number of X-ray crystallography structures for potential drug ttargets would make it possible to see how small fragments bind the proteins."

Instead of searching fragment libraries with HTS, scientists screen them with biophysical methods, like mass spectrometry, nuclear magnetic resonance, surface plasmon resonance, or X-ray crystallography. "These methods are used because fragment molecules generally bind rather weakly and are so small that it's hard to predict where they might bind," Cohen explains. So the analytical techniques must provide more resolution.

As reported in a 2017 issue of the Journal of Medicinal Chemistry, Cohen, along with Walter Fast of The University of Texas at Austin and their colleagues, applied FBDD to find new inhibitors of New Delhi metallo-β-lactamase-1 (NDM-1), which reduces the efficacy of β-lactam antibiotics. As Cohen explains, "We ran a screening campaign using libraries developed in our lab, and we found a novel core scaffold that bound to the active site of NDM-1." The team confirmed the binding and developed that into a lead-like molecule.

There are few areas of pharmaceuticals that are in as much need as antibiotic development. With increasing resistance among infectious diseases, any technique that turns up more lead molecules should be explored.

ADDING IMPROVEMENTS

Although FBDD already provides pharmaceutical scientists with more capabilities, this technology can be further refined. For example, Astex focuses on only FBDD, but it collaborates often with pharmaceutical companies that use HTS. "That's a particularly powerful method," Rees says.

To make FBDD's technology even more powerful, Rees sees several technologies that could be improved. For one thing, better technology to screen for fragments that bind targets even more weakly would help scientists find new potential lead candidates, and then their binding strength could be improved with further molecular modifications. "Plus, an increasing number of X-ray crystallography structures for potential drug targets would make it possible to see how small fragments bind the proteins," he says. "Then you can grow the fragment into a lead in a very efficient way."

As Cohen concludes, "A fragment-based approach is a good area to help people find new compounds that, maybe, they couldn't find by other methods."

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FORENSIC PROTEOMICS

A GROUND-FLOOR OPPORTUNITY

by Angelo DePalma, PhD

Where DNA fingerprinting has been used for many years in forensics, proteomics represents a new frontier in forensic science. Though still a young field, proteomics brings a broad, deep tool set to investigating thorny forensics problems.

Scientists may argue whether genes or proteins are more physically robust under specific circumstances, but a consensus is forming in favor of proteins in many forensics settings. "Emerging next-generation proteomics provides much more detailed information than genomics about the evidence in question," says Oscar G. Cabrices, PhD, staff scientist at SCIEX (Redwood Shores, CA). "Mass spectrometry of proteins can provide associative paths between body fluids and actions, times, and sample transfer paths within collected evidence." Instead of simple yes/no answers (e.g., whether a gene for a particular organism is present), proteomic analyses become more molecularly specific and more amenable to comparative associations, and provide a sounder scientific basis for drawing conclusions.

However, proteomics is not without its issues. The two knocks on proteomics compared with genetic analysis are the lack of a process for protein amplification analogous to polymerase chain reaction (PCR) and the high cost and operational complexity of proteomics.

True, PCR can amplify genes from samples too small to analyze directly. That very amplification power, however, is prone to interference, particularly when a sample touches several individuals or other organisms. PCR also requires that one know what to look for.

Cabrices notes another limitation of genetic analysis: "Single DNA analysis cannot indicate which fluid the genetic material originated from. Identifying which fluid or fluids are present in an evidence sample can be instrumental in determining events of a suspected crime." DNA analysis is typically performed through capillary electrophoresis (CE) with spectroscopic detection. "As far as other separation techniques are concerned, LC [liquid chromatography] and CE are complementary, but their hyphenation to mass spectrometry [MS] for forensic protein analysis increases the potential to deliver much more conclusive information," he adds.

Vendors often bundle instrumentation into systems around specific workflows such as analysis of environmental pathogens or pathology samples. Routine forensic proteomics would include an LC-MS/MS system with automated sample preparation capabilities for enhanced sample chain of custody; a discovery research system might be built around a quadrupole time-of-flight mass spectrometer.

"Forensic proteomics is quickly growing, and we are working with top researchers in the area to innovate the base technology," Cabrices says. "But we'd like to see how the routine forensic scientists embrace next-gen serology, with the vision of evolving their routine approaches to plug-and-play, MS-based analysis methods."

In other words, it is too early to consider proteomics workstations built around forensics.

WHERE IT BEGAN

In 2012, a group at John Jay College of Criminal Justice in New York published a paper describing a shotgun proteomics approach to analyzing the immune response of a 500-year-old Incan mummy. Lead author Angelique Corthals reported that a lung swab from the deceased harbored the remnants of *Mycobacterium*, a pathogenic pulmonary agent that could cause death.

Conventional analysis, including PCR (how the bacteria were detected in this case), does not answer definitively. This individual may have died from pulmonary infection, or been sick from it but died from some other cause, or not been sick at all when he died. Luckily, Corthals had another, similarly preserved mummy from the period who did not harbor *Mycobacterium*. Using mass spectrometry, specifically a Thermo LTQ-Orbitrap XL instrument, investigators compared immune system proteins from the putatively healthy and infected decedents. They also examined blood samples from the mouth of the mummy harboring the bacterium.

The proteins analyzed from this individual indicated that he did not suffer from an active infection, and that the blood in his mouth resulted from trauma—which may have been the cause of death.

Corthals wrote that conventional methods of characterizing immune reactions to pathogens, such as antibody-binding immunoassays, "require fresh tissues, use a small number of targeted antibodies, and are prone to both false positives and false negatives." Proteomics identifies and quantifies proteins directly. Proteins outlast DNA by some accounts, do not require amplification, and represent a wider swath of physiology.

Corthals' study leaned on earlier work on DNA fingerprinting and later attempts to apply the young science of proteomics to pathogen detection. She took this idea to the next level, toward the study of physiologic events concurrent with infection. And perhaps without realizing it, in this one paper Corthals both demonstrated and laid the philosophic foundation for forensic proteomics.

"Proteomics brings a broad, deep tool set to investigating thorny forensics problems."

SPECTROSCOPIC IMAGING

Blood detection and characterization are normally conducted through optical, spectroscopic, and chemical methods. Optical techniques are the least destructive, but spectroscopy (e.g., short ultraviolet) sometimes degrades DNA. Chemical analysis always alters/destroys the sample, often involves sample preparation, and may be incompatible with the circumstances or environment in which the sample exists. None of these test categories is particularly helpful in distinguishing between human and animal blood.

Simona Francese, a scientist at the Biomolecular Science Research Center (Sheffield Hallam University, Sheffield, UK), addresses the shortcomings of standard analytic crime scene investigators and crime lab techniques through bottom-up *in situ* proteomic mapping of multiple blood signatures through matrix-assisted laser desorption mass spectrometry imaging (MALDI-MSI).

Analytical chemists employ MALDI, a "soft" MS ionization technique, on proteins and other biomolecules that do not survive hard ionization methods. MALDI is also attractive in forensics for its avoidance, in many cases, of lengthy sample preparation.

Francese combines MALDI with ion mobility MS, which separates isobaric ions based on their "drift time," thus adding robustness and reliability to molecule identification. MALDI-MSI allows the imaging of complex biologic details of intact tissue—in this case, the distribution of chemicals within the fingermarks—without the use of antibodies or radioactive labels. The technique instead employs trypsin digestion of the sample *in situ* followed by MS visualization of defined regions within the mark.

In the non-proteomics study of stains made from horse and cow blood, MALDI-MSI detected heme molecules from both samples and distinguished hemoglobin from the two species. Then, using proteomics, the group was able to distinguish horse from human hemoglobin using multiple blood signatures.

The proteomics method is compatible with acid black 1, ninhydrin, and acid yellow 7 methods, which are common crime scene investigation blood print analysis techniques.

"Crime scene and crime lab methods are presumptive because the tests are not overly specific for blood," Francese explains. "For example, egg yolk reacts to a certain blood reagent exactly like blood does, and that would be a false positive."

An example of confirmatory tests are immunogenic tests, which are expensive and destructive, or the MS method described above. In some cases, MALDI is superior; for example, in identifying false positives from the reagent-based tests.

NOT DODGING THE BULLET

Investigating a crime or law enforcement scene where multiple shots have been fired entails assembling visual and physical evidence into a credible narrative. Analysis of DNA remaining on bullets can help identify which bullet struck which participant, but it provides little or no information about which round caused specific tissue damage. Moreover, genetic material degrades rapidly. Connecting a bullet to a specific organ is essential for determining which round caused injury or death, a fact on which criminal prosecution (or defense) may rest.

Dr. Sascha Dammeier and his coworkers at the University of Tübingen (Germany) have reported on a method that uses mass spectrometry to generate organ-specific protein expression profiles that could help determine a bullet's path through a human body. The method involves digesting protein on the bullet surface followed by peptide mapping.

Dr. Dammeier constructed a database of organ-specific protein profiles from five cow organs: heart, lung, kidney, liver, and muscle. He used a bullet simulation to collect

material, and then analyzed the samples through lengthy LC-MS analysis. This provided classifiers for each organ, against which researchers could compare real-life samples.

Unfortunately, this approach resulted in significant misidentifications using bullets from an actual crime scene, in part due to bullets penetrating multiple organs. "We were unsuccessful because the amount of data collected was insufficient to run the computational methods required to identify organs," Dr. Dammeier says. Switching to a top-down (intact protein) approach was more successful, because now the organ identification could be made on the basis of organ-specific proteins.

On the question of the physical robustness of DNA versus protein, Dr. Dammeier is more philosophical than some experts, saying, "Longevity strongly depends on humidity, temperature, and other factors." Since proteomics is the only way to determine organ of origin, its persistence is therefore irrelevant. Even so, one would need to characterize protein expression beforehand in various organs, which involves analysis of the protein itself or of the transcriptome (RNA). But RNA is very short-lived, whereas protein persists for weeks even under adverse conditions.

Initially, the Tübingen group used a hand punch to simulate a bullet passing through flesh and organs. However, shear forces for projectiles traveling 600-700 m/sec (or faster) are difficult to generate by hand. With the assistance of local police, Dr. Dammeier's group was eventually able to incorporate actual shooting into sample collection. "The material collected was sufficient for a direct classification of more than half the organs, but the results were not as clear as with the punching experiments," he explains.

Could this difference be explained by the bullet's much higher velocity, or the heat it generated, relative to a manual punch?

Dr. Dammeier thinks not: "In real shootings, the contact time of the bullet with the organ is shorter than with the manual punch, resulting in less collected material. We do not believe that speed has any other effect on the sample." One reviewer actually asked him about heat generation in the bullet's path, but Dr. Dammeier assured him that there was none worth reporting.

THE FUTURE

Proteomics is by no means an established approach for solving forensics problems. Proteomics has a reputation for being instrument- and expertise-intensive, time-consuming, and requiring a high level of computational acumen.

Dr. Dammeier admits that "there's not much out there," while noting that further evolution of mass spectrometry toward greater portability, screening capability, and user-friendliness will help expand that instrument's role in forensics, as it already has for the detection of illegal drugs, toxicology, and pesticide analysis.

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Saptashati "Tania" Biswas

ASK THE EXPERT

LC-MS-MS AND GC-MS FOR WATER QUALITY MONITORING

by Rachel Muenz

Saptashati "Tania" Biswas is a postdoctoral research scientist at the National Center for Water Quality Research, which is based at Heidelberg University in Tiffin, Ohio. She received her BSc at the University of Calcutta, MSc at the University of Kalyani, and PhD at the University of Maryland, College Park. Her primary research focus is on analytical method development of environmental contaminants such as pesticides, insecticides, antimicrobials, and other chemicals of emerging concern.

Q: What does your laboratory do?

A: Our lab has two major goals, which are monitoring and researching chemicals in the Lake Erie watershed and beyond. We are a leader in surface and groundwater research and monitoring, and our mission is to promote the sustainable use of water and soil resources while striving to protect ecosystem integrity. Whatever we do is basically surrounding this whole mission of sustainability, and understanding the use and changes in the management practices of these chemicals.

Q: What do you use mass spectrometry for in your work?

A: Mass spectrometry (MS) is used in inductively coupled plasma (ICP-MS) for doing metal analysis in groundwater and well water. Our gas chromatography-mass spectrometer (GC-MS) is a Varian [now Agilent] and is used for our pesticide monitoring program, which started in the 1980s and now monitors more than 20 pesticides. Our suite of pesticides includes triazines, acetanilides, organophosphates, dinitroanilines, and carbamates. We are using our liquid chromatography-triple quadrupole mass spectrometer (LC-MS-MS) to develop new techniques for measuring glyphosate and acid herbicides. These are the newer pesticides that are of great interest and have not been extensively monitored in the Great Lakes watershed.

Q: Can you tell me a bit more about that LC-MS-MS work?

A: The major focus is developing research projects around the new glyphosate and acid herbicide methods. We don't just measure these compounds like other analytical labs would do, we do research based on the data. So, we develop hypotheses and objectives, and write proposals to get grant money to do research. For example, for the glyphosate method that we are developing right now, we are trying to analyze trends based on the precipitation patterns in this area and compare different types of watersheds. So, there's an environmental and watershed management aspect to whatever chemical analysis we do. Similarly, we are doing comparisons with acid herbicides, which are also present in this area. Our research projects are focused on developing these methods on the LC-MS-MS, and then answering questions related to water management and water-related issues and understanding concentration and loading. Glyphosate is a tricky compound to measure; it's a very polar compound so there is no specific column that has worked for everyone. For us, we have to have a very high-throughput method because we analyze hundreds of samples per year. We produce a lot of data, so we are not interested in derivatization and doing complicated methods with complicated workflows. At this point, we are trying to figure out the shortest method we can use for QA/QC. We're working on improving the workflow and making it faster.

Q: How do you go about developing methods for your work?

A: When developing a method, first we decide which compounds we are going to target. How important are they and what research projects can be developed around the method development? After selecting our analyte(s) of interest, we study its chemical properties and research suitable LC-MS conditions. In a multiresidue method, we can analyze different chemicals simultaneously and that saves a lot of time. We initially wanted to make the glyphosate method a multiresidue method, but unfortunately glyphosate has its own chemistry. So, we first figured out what kind of MS conditions it would need, then did the MS optimization and went to the LC. We test out different kinds of columns and select the best column that will give us good separation and resolution. We also optimize other important LC parameters, such as mobile phases, internal standards, flow rates, and injection and wash volumes—all the usual LC-MS parameters.

Q: What is most important in developing those methods?

A: Because we are producing a lot of data, the most important thing is how to minimize the time and have a high-throughput method. For example, for glyphosate we already have a method that will work, but it requires several extra steps and we don't want to spend that much time for every sample because we have a large volume of samples coming through. So, there are always challenges—how do we reduce these steps, is there a column that will help us extract or separate these chemicals without having them go through all these steps? We always try to see how we can save on time and chemicals.

Q: What recent trends in mass spectrometry have you seen?

A: I see many labs having diverse needs of instruments as they are analyzing different suites of chemicals. So, we have a front-end that is the chromatography part—LC, GC, or IC—and then we have the back end that is the mass spectrometry part, which is a triple quad, time-of-flight, or an ion trap mass spectrometer. Scientists are experimenting with switching around the front-end and the back end, depending on which compound they are analyzing. For example, if they have an LC front-end, they will try to switch that with IC, so they can analyze a different class of compound or do a different kind of experiment. Not every instrument can be switched around, but this kind of capability is increasing to give MS a more versatile application. And there are also newer columns that are always being developed, especially for polar compounds. Ten years ago, we had to derivatize almost every compound and now we can do a straightforward analysis without going through all these derivatizations because [of the] newer columns and compatible extraction cartridges.

Q: What are the key challenges you face in your work?

A: There are always maintenance problems. Unlike simple instruments [such as] spectrophotometers, [mass specs] need a lot of maintenance because they are very sensitive, in that we are analyzing compounds that are at parts-per-billion or parts-per-trillion levels. The room has to be really clean, and if there is some kind of an incompatible buffer that is introduced by error, then it's a problem. There are certain ions we don't ever want to introduce into the mass spec, because you cannot clean out the inside of the mass spec very easily. It requires technical help. Therefore, when we are developing a method, we are very conservative in using the mobile phases.

Q: What are some of the plans for your lab's future?

A: One of the things we did recently is purchase our LC-MS-MS to analyze new classes of compounds that we weren't measuring before. After completing the glyphosate and acid herbicide projects, we plan to develop methods for microcystins. A microcystin is an active toxin in harmful algal blooms. We are in the Great Lakes watershed, and the Western Lake Erie Basin has a lot of algal bloom problems during the summer. Being in this region, we are always requested to analyze microcystins and that's not compatible with the current methods. We have one machine, and we have all these different classes of compounds that we want to analyze, so once these projects are done, we would like to analyze microcystins. Apart from that, we also want to buy an accelerated solvent extractor that will improve our sample preparation. Right now, we have cartridges and disks that have to be manually treated and eluted, so there has to be a technician dedicated to both the separation and preparation of compounds.

Q: What advice do you have for those who are just starting in environmental labs?

A: To those who are in the process of setting up a new lab, I would first recommend choosing the companies you are buying your instruments from very wisely, especially the expensive instruments like the GC-MS and LC-MS, because the relationship doesn't end after buying the instrument. It's a long-term relationship because these instruments require a lot of maintenance and troubleshooting—especially if someone is new to environmental sample analysis. Having reliable customer support from the company is very, very important. Some companies are very bad with customer service and you will not get any help, and some companies will be so helpful that they will almost act as your partner in the process and help you with the troubleshooting. I would suggest attending relevant scientific meetings, for example, ASMS, where you meet many vendors. Have a good discussion and clear expectation as to how much of their involvement you will need, especially if you don't have any experience. Not many people consider that—they go with the cheapest instrument, but cheapest is not always the best. You want to use these instruments long-term—at least for five to 10 years—so be wise in choosing which brand you want. I've learned my lesson. Now, when I'm buying an instrument, I have so much discussion with customer support and technicians. There are so many companies and it's a competitive market—the customer has a lot of power; it's just that we have to realize that it's in our hands to choose the right brand.

***Rachel Muenz**, associate editor for* Lab Manager, *can be reached at rachelm@labmanager.com or 888-781-0328, x233.*

SPECTROMETRY

ANALYZING DNA AND PROTEINS *IN VITRO* AND *IN VIVO* WITH ULTRAVIOLET-VISIBLE SPECTROSCOPY

by Angelo DePalma, PhD

As high-performance liquid chromatography and mass spectrometry have become more accessible, ultraviolet-visible (UV-Vis) spectrometry has fallen out of favor for detailed chemical analysis. Sensitivity and resolving power are the main reasons.

In their native state, molecules that do not possess a chromophore that absorbs within the appropriate wavelength range will be invisible to UV-Vis. Proteins, DNA, and RNA have such chromophores (as do some viruses and bacteria), but unbound sugars and lipids do not. In practice, to achieve the sensitivity demanded by modern science, even genes and proteins must undergo derivatization.

A perusal of the literature shows that when leading-edge biochemistry employs UV-Vis spectrometry, it usually does so as the detector stage of a separation (usually LC), or built into a microplate reader. Thus the "spectroscopy" occurs not as the main event within a cuvette, but at the very point of scientific interest.

Within these settings, the detectors in plate readers are capable of performing point measurements, time courses, kinetics, and other experiments in reproducible formats. UV-Vis is much more limited when acting as an LC detector, but the resolving power of chromatography opens doors to other types of analyses, particularly involving the resolution of species with very similar absorptions.

Through the plate, brightly

DNA quantitation is critical for many samples containing low quantities of genetic material. Forensics and next-generation sequencing (NGS) come to mind. In NGS, the investigation of mutations, for example, requires knowledge of precise DNA levels.

Fluorescent methods have proved to be accurate and sensitive, as a group at BMG Labtech showed in a recent application note. As the indicator dye, the scientists used the AccuBlue™ NextGen dsDNA (double-stranded DNA) detection kit from Biotium for its sensitivity, and BMG's CLARIOstar® microplate reader.

AccuBlue demonstrated perfect linearity in the dsDNA range of 1 to 5,000 pg (correlation of 0.99983) in 96-well plates. The assay performed even better at the six lowest concentrations, with a linearity of 0.99998.

"The optical system of the CLARIOstar was vital to obtaining these results," notes Carl Peters, PhD, applications scientist at BMG Labtech. "Wavelength selection through a linear variable filter system enables filterlike performance while being selective for any wavelength and bandpass up to 100 nm." The wavelength selection is paired with a linear variable dichroic that automatically uses the best dichroic for optimal transmission of excitation light to the sample and subsequently emission light to the detector.

AccuBlue detects only dsDNA, so contamination from ssDNA, RNA, and proteins will not affect accurate quantitation, regardless of the source. Furthermore, it destroys the sample, so unlike reagentless UV detection, it cannot be used for any subsequent purpose. But the sample size is small, so losses are minimal, according to Peters.

"We routinely see similar correlation coefficients for any assay type that uses a standard curve that conforms to a linear fit," he says.

Only skin deep

Detecting biological molecules *in vivo* is arguably one of the great challenges of biomedical science. Clinical and basic research are limited to sampling, which in some cases is difficult, in others impossible, and in all cases disturbs the natural environment in which the molecule exists.

A group at Ocean Optics (Largo, FL) has recently demonstrated a method based on visible and near-infrared reflectance spectroscopy to determine the "melanin index" and "moisture index" of skin by measuring levels of melanin and water, respectively, at strategic locations in the skin. They used a dual-spectrometer design and compact diffuse reflection

probe with built-in light source to measure diffuse reflectance from tissue across the visible and near-infrared regions.

The first step was to establish parameters for melanin concentrations. Although melanin is not a distinct compound with a perfectly resolvable spectrum, it may nevertheless be quantified in skin spectroscopically through chemometric analysis. The two major potential interferences, highly-absorbing hemoglobin and deoxyhemoglobin, absorbed strongly below 450 nm and showed characteristic peaks between 520 and about 580 nm.

Investigators avoided the strongly absorbing regions for the hemoglobins and settled on four wavelengths for quantifying melanin: 400, 450, 490, and 700 nm. Combining absorbances at these wavelengths provided a simplified method for melanin index, which correlated closely with predicted values based on skin color. Moisture index was more straightforwardly generated by its strong absorbance peak at 1465 nm (in the NIR), referenced against a dip at 1300 nm.

Yvette Mattley, PhD, a principal applications scientist for Ocean Optics, describes the study as a proof of concept. "Our goal was to inspire others with an example of the types of analysis that can be done with diffuse reflectance spectroscopy. In a real-world setting, a robust model for outputting accurate tissue properties would require measuring reflectance from the skin of hundreds of people, at multiple locations on the body, to provide data for skin with a wide range of tissue properties."

Extracting significance from measurements like these would require comparing reflectance spectra from collected samples against reference values. "With the wide range of tissue compositions possible, the work to develop robust versions of these indices would be very extensive, potentially requiring months of work, depending on the resources available. Such a model should then be general enough to be used for measurements on many individuals without additional analyses."

Light interacting with tissue, blood, and other biological materials reveals an abundance of detailed information. "And it does it all noninvasively, in real time, and often, at lower costs per measurement than other methods," Mattley says.

Actual spectroscopy—the detection or characterization of specific biomolecules vs. sensing of physical phenomena—is more problematic, but by no means impossible.

For the exploratory measurements described here, Ocean Optics used a combination of two spectrometers covering the visible and NIR regions from 400 to 1600 nm (FLAME-S-VIS-NIR and FLAME-NIR). This maximized the data collected and provided a wide wavelength range to analyze for tissue characterization. Once key wavelength regions are identified, the measurement system could be configured to measure spectral data in the key regions of interest. Diffuse reflection was collected from the skin using a probe with a standoff accessory (TC-DR-PROBE) to ensure consistent sampling geometry throughout the measurements.

▲ *A scientist at Ocean Optics quantitates melanin, hemoglobin, and deoxyhemoglobin using a simple handheld spectrometer.*

"Setting up the equipment for these measurements is straightforward," Mattley explains. The user simply connects the spectrometers to the reflection probe using a bifurcated optical fiber. The measurements themselves are also relatively easy, but require a very consistent sampling geometry between the probe and tissue under analysis. The angle and distance between the probe and skin must be maintained from the time the reference is measured throughout the sample measurements to ensure accurate spectral data.

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FOR ADDITIONAL RESOURCES ON UV-VIS FOR SPECTROMETRY, INCLUDING USEFUL ARTICLES AND A LIST OF MANUFACTURERS, VISIT WWW.LABMANAGER.COM/UV-VIS

WHAT DO GAS CHROMATOGRAPHY USERS HAVE TO SAY?

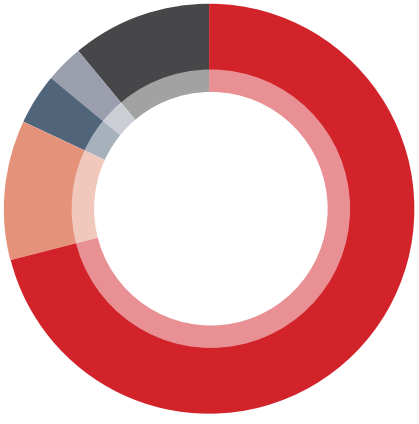
Gas chromatography (GC) is a common technique used in analytical chemistry for separating and analyzing compounds that can be vaporized without decomposition. GC is typically used for separating the different components of a mixture, improving the purity of a particular substance, or identifying a particular compound. GC is a ubiquitous technique, and the various GC instruments available are designed to achieve every requirement of the technique.

Survey respondents reported the following problems when using their GC systems:

Retention time shifts	**51%**
Baseline disturbances	**46%**
Irregular peak shapes or sizes	**40%**
Loss of separation or resolution	**40%**
Ghost peaks	**24%**
Broad solvent fronts	**21%**
Quantitation problems	**17%**
Rapid column deterioration	**10%**

For those planning to purchase a new GC system, the primary reasons for the purchase are as follows:

Replacement of aging system	**71%**
Addition to existing systems, increase capacity	**11%**
Setting up a new lab	**4%**
First time purchase	**3%**
Other	**11%**



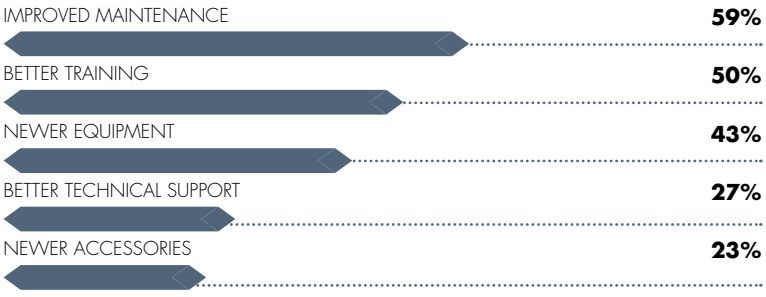
TOP 6 QUESTIONS

You Should Ask When Buying a GC System:

1. What factors come into play when determining the GC system specifications you require in terms of cycle time, enhanced operator benefits, increased productivity, and flexibility for specific applications?
2. What differentiates the vendor's GC system from others offered, in terms of performance?
3. How do you validate the specification claims presented by the vendor?
4. Has the data processing software been designed for enhanced analytics, with workflow in mind and does it support critical compliance requirements?
5. What are important price points to keep in mind when selecting a GC system?
6. Laboratories need fast and effective services, including an effective distribution of instruments, spare parts, education, and service personnel. How does the company serve these needs worldwide?

FACTORS

That Would Help Users Overcome Their GC Issues:



Some of the most exciting applications of GC, as reported by survey respondents:

- Discovery of new proteins
- Drug testing
- Portable GC for field work
- Flavor profile investigations
- Pesticide analysis

For more information on GC systems, including useful articles and a list of manufacturers, visit www.labmanager.com/GC

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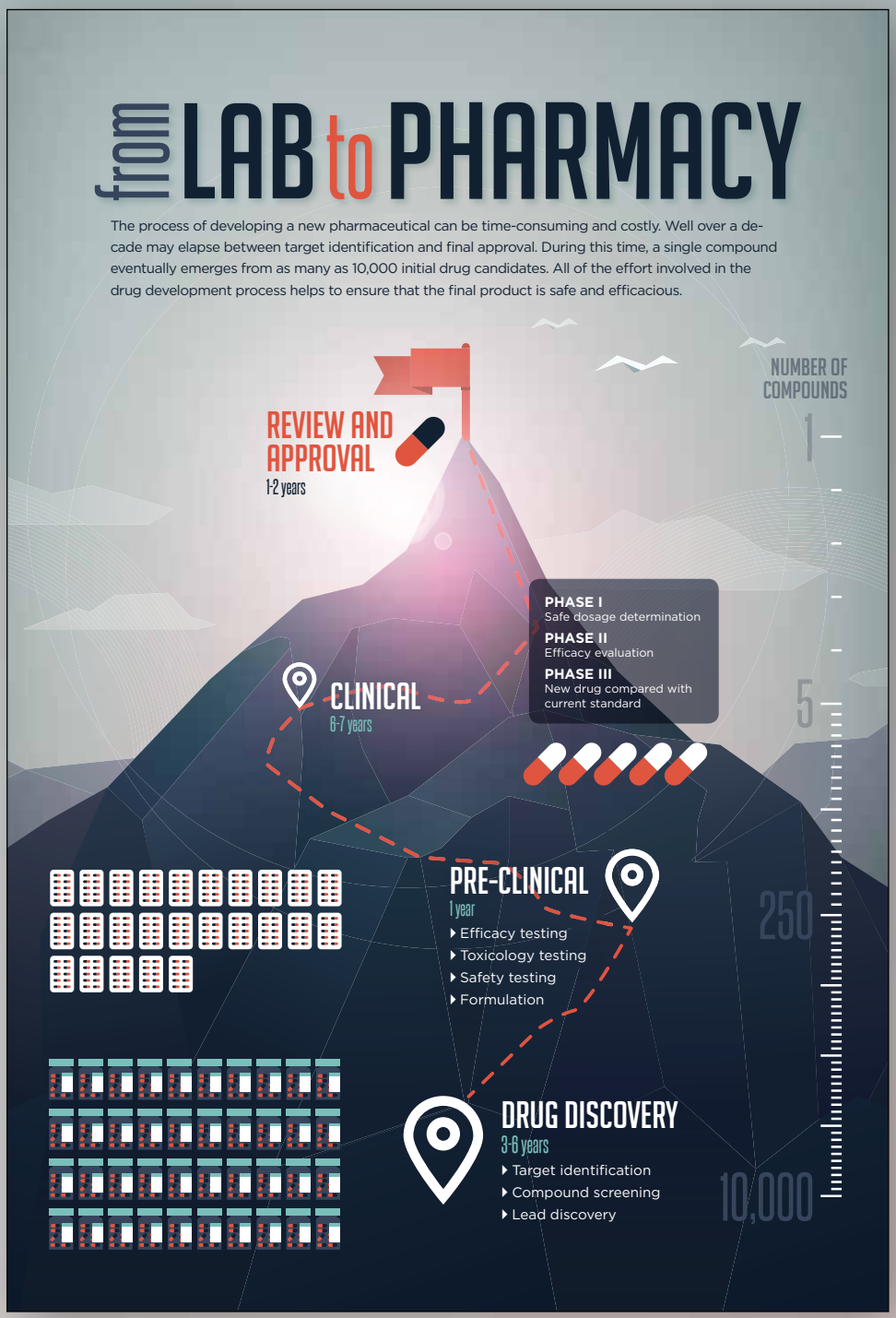


Michelle Lowe Ocaña

ASK THE EXPERT

ADVANCES IN IMAGING

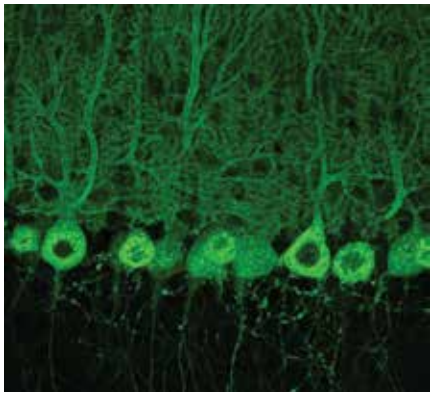
by Tanuja Koppal, PhD

Michelle Lowe Ocaña, senior imaging specialist and manager of the Neuroimaging Core Facility at the Harvard Medical School, talks to contributing editor Tanuja Koppal, PhD, about new technologies and trends in imaging hardware and software that are impacting what she does in her lab. She points out some areas that still need improvement and offers useful advice on what to look for and how to think strategically when upgrading or investing in new imaging systems.

Q: What are the imaging techniques commonly used in your facility and for what applications?

A: Our facility supports a wide range of researchers. Our current popular systems are the confocal microscopes, array tomography, and the whole slide scanners. Whole slide scanning—where the tissue is cut into sections and imaged—has become the first step in basic science. The ability to see an entire organ in slices has completely transformed how basic research is done. A researcher can look at an entire brain and see where a single neuron is connected to another, how disease starts or spreads. Scanning and saving whole slides also has an advantage over glass slides for archival purposes, as the samples can be saved and accessed remotely. Confocal microscopy allows the researcher to optically section each tissue to view processes and metabolites within individual cells. It allows researchers to determine where a protein of interest is located within an individual cell, as well as within an organ.

Array tomography is an imaging technique that creates super-high-resolution volumes of tissue. The technique requires the tissue to be embedded in a plastic resin to maintain structural integrity. The plasticized tissue is cut into ultrathin (50-200 nm) serial sections using a diamond knife and then mounted on a glass slide. Each slide can have a ribbon of a hundred sections of tissue concatenated together. Antibodies are added to the slide to attach to precise protein targets. The serial sections are



▲ *Cerebellum captured on Olympus VS120 Virtual Slide Scanning Microscope (Source: Stephanie Rudolph PhD, Wade Regerhr Lab, Department of Neurobiology, Harvard Medical School)*

imaged using basic fluorescent microscopy and the resulting images are compiled into a volume stack. The tissue can be eluted with chemicals that will remove the antibodies, and restained with new antibodies for other protein targets. The process is repeated until the tissue is spent of all antigenicity, or until all the proteins of interest have been identified and imaged. The end result tells the researcher exactly where a protein is within the volume of the slice and exactly where it is in relation to all the other proteins imaged.

Q: What changes/improvements have you seen in imaging hardware and software in recent years?

A: There have been so many improvements in imaging over the years that it's hard to keep track of them all. Overall, hardware has become cheaper, smaller, and more efficient. Imaging cameras have become faster and more sensitive. Pixel technology has grown and changed so much that it's hard to imagine that sensitive collection of photons was out of reach for most researchers just 10 years ago. I can now buy for under $40,000 a camera that can capture 80 percent of the photons with a frame speed of 100 fps. Lasers and laser combiners have become smaller, less expensive, and easier to integrate. I used to have a bunch of gas lasers with all kinds of fans pushing the heat out of the room. The lasers needed to be internally aligned and the gas had a relatively short lifetime. Today, I can buy a laser online that fits in the palm of my hand and will last at least twice as long as the old gas tubes, and it will put out minimum heat load.

The biggest change in technology, however, is in the software and the computers that drive it. It's mind-blowing how quickly computers have evolved. My facility can't run without them. Everything is software driven. Every year computers improve in speed, drive space, graphics capabilities, and cost. These improvements directly affect how we image things and how we view imaging as a tool. More hard drive space means we can collect more data, and improved speed to write and transfer helps us collect that data faster. Software has had to keep up with the exponential growth for imaging and computing faster, bigger, and more data.

Q: What are some areas that still need improvement?

A: Transfer speed is an area that still needs improvement. In some of our

equipment, the software is designed to acquire images slower than the hardware can run because of the transfer speed from our imaging systems to the computer hard drive. Large data analysis is also a bottleneck. Big data is growing exponentially and becoming mainstream in research. That ability to store, retrieve, and measure the data collected can be very expensive and time-consuming.

Q: Are there any specific concerns with sample prep or post-data analysis that you think readers should be aware of in imaging?

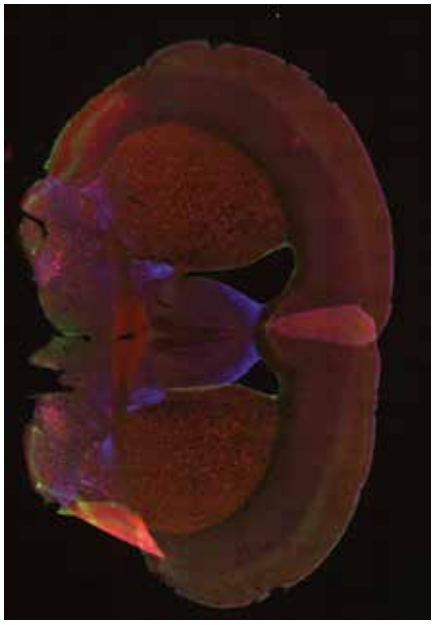
A: In regard to sample prep, little things add up. Paying close attention to small details has big payoffs at the end. Don't rush it and keep it clean. Every single step deserves your undivided attention, from cutting to sealing the coverslip.

Make sure you have a good system to name your samples when saving them for future use. Coming up with smart, easy-to-read naming keys for your samples will improve your science and make it easy for you to find your data quickly without having to repeat experiments. Make a naming key, stick with it, and put it everywhere. Being proactive and consistent with your naming protocol will make you a hero in your lab long after you are gone.

Know the bit-depth of your image acquisition system and use the full intensity range. Too many times, researchers spend countless hours creating images that cannot be accurately measured because they are out of range.

Q: What are some of the trends you are seeing in technology or in applications for imaging?

A: Some trends in imaging that I have seen in recent years include the use of high-content and super-resolution imaging. Collecting whole slides in the case of slide scanner imaging and imaging entire organs or organisms—using technology like light-sheet imaging—are quickly becoming fundamental in biology. These technologies provide a



▲ *Saggital section captured on Olympus VS120 Virtual Slide Scanning Microscope (Source: Jessica Saulnier, Bernardo Sabatini Lab, Department of Neurobiology, Harvard Medical School)*

macro to micro view of our biological world. Pairing this with super-resolution techniques such as Stochastic Optical Reconstruction Microscopy (STORM), Photo Activated Localization Microscopy (PALM), Stimulated Emission Depletion (STED), and Structured Illumination Microscopy (SIM) grant researchers the opportunity to image at the molecular level. Using different modalities together on a single project could provide a clearer picture of disease within an organism from the basic morphology to molecular biology.

Q: Any advice to readers who are looking to invest in or upgrade their imaging equipment?

A: There are a lot of things to evaluate when considering your next hardware purchase or upgrade. Technology and hardware change so quickly. The most important consideration is to make sure you buy the system that is most compatible with your research. We all are dazzled by the newest and coolest gadgets, but these often come with undeveloped software and may not have real-life applications in your science. Think hard before purchasing a module or system that is cool, but that you "might" use. The software is as important as the hardware. That said, it's really all about the optics. You need to resolve your particle. Spend the money on high numerical aperture lenses, especially when purchasing a confocal or high-resolution microscope. Also, spend the time learning the ins and outs of the system. Take it apart or have the service technician take it apart for you. Look inside; consider the layout and the moving parts. Moving parts will fail eventually. Are there a lot of them? Will you need to budget for that in the future when they reach their lifetime? How quickly can it be serviced? Are these parts readily available or is there a lag in manufacturing and shipping?

If investing in a new system, you want something that is upgradeable, flexible, and useful in your lab. You are going to purchase a very expensive piece of lab equipment, so make sure it's something that your lab will use a lot. If it's going to be used a lot, you will need to purchase something that can't easily be broken. Accidents happen. A system that is well manufactured will take that into account and have built-ins to minimize catastrophe. Always consider upgrading before buying something new. I purchased a Laser Scanning Confocal Microscope six years ago. I upgraded the optics and scan galvo for better transmission and added an autofocus module when live-cell confocal imaging was becoming an important part of our science. I added a stage with mosaic tiling when large volumes of brain slices were needed. My system can grow with the needs of the community without the need to raise significant capital. This was important to my core lab and me.

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CO_2 INCUBATOR

TECHNOLOGY AND TECHNIQUE KEEP CULTURES CLEAN

by Mike May, PhD

Any scientist who has spent even a bit of time working with cell cultures has probably contaminated some—more likely lots—of them. Keeping cultures free of contamination depends on technique and the right tools. In the best case, those tools keep scientists out of trouble as much as possible, and the right carbon dioxide (CO_2) incubator can do just that.

If contamination arises, the first thing to figure out is the source. "Contamination in CO_2 incubators nearly always comes from outside the incubator," says Mary Kay Bates, senior global cell culture specialist at Thermo Fisher Scientific (Waltham, MA). "Most commonly, the sources of incubator contaminants are humans working in the lab, and environmental contaminants that come in with humans." Some of that can't be avoided, because we are basically microbe machines, shedding them from our hair, skin, and even breath. No amount of technique, even the most artsy of all, can keep all those microbes out of an incubator.

"The simple fact is that when any incubator door is opened, the air inside mixes with the surrounding room air and that's often how contaminants get inside," Bates explains.

Timely turnover

To keep as many microbes as possible out of a CO_2 incubator, air coming into it must go through a HEPA filter. But that's not enough. "Thermo Scientific CO_2 incubators filter the entire chamber air volume every 60 seconds to establish ISO Class 5 cleanroom conditions in five minutes after a 30-second door opening," Bates notes.

To keep everything in an incubator clean, it takes an engineered design. Buckner Richerson, vice president of international sales at NuAire (Plymouth, MN), asks, "A forgiving incubator design assumes that contamination is coming, so what happens after that?" In a well-designed CO_2 incubator, filters keep particles and microbes from entering the chamber. Most incubators include in-line filters for incoming air, CO_2, oxygen in an oxygen-sensored incubator, the main capsule, and one for the electronics.

Seeking sources

Despite the sophisticated technology in today's CO_2 incubators, don't expect them to do everything. Help an incubator out!

"Be careful about technique and where you do prep," says Richerson. If that technique contaminates a Petri dish or multiwell plate, the microorganisms will then grow inside the incubator.

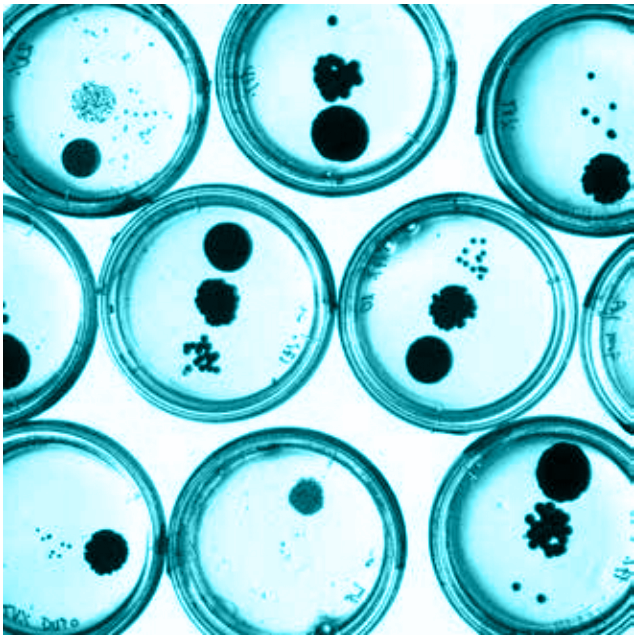
> "The simple fact is that when any incubator door is opened, the air inside mixes with the surrounding room air."

Part of that technique involves incubator placement. Keep a CO_2 incubator away from windows that are opened. Even keep it away from doors, or as far from them as possible. It's even more difficult to keep an incubator away from air vents, but worth doing, because that air carries contaminants. "A common source of fungi, for example, is when a building air duct in the lab ceiling is blowing cooled air onto the incubator," Bates explains.

That's just the start. Stacks of cardboard boxes can get damp and breed mold. Other equipment in a lab can also start a chain reaction of contamination. "Users should clean other cell-culture equipment, such as centrifuge chambers and rotors, microscope stages, and water baths," Bates encourages.

In general, clean everything. Some scientists use the top of an incubator as a shelf for storing gloves or other items, but that area can then harbor microbe-carrying dust, poised to sprinkle into an open incubator door.

In addition to the air, dust, and samples that go into a CO_2 incubator, water can also cause contamination. "If nonsterile water is added to the humidity pan, this is a clear risk for introducing microorganisms, because even distilled water is not sterile," Bates points out.



Tidy tips

To keep a CO_2 incubator clean, follow tips from the experts. It starts with technique. Always follow aseptic techniques, such as wearing gloves when touching an incubator.

Keep it clean. "Clean and disinfect the incubator regularly, at least once each month," Bates suggests. "Discard old, unused cultures, clean up any spills, and wipe with 70 percent ethanol and allow to air dry." The ease of cleaning an incubator depends largely on its design. A one-piece interior with coved corners is easier to clean. "You want a surface with no crevices or cracks," Richerson says.

At PhoenixSongs Biologicals (Branford, CT), executive vice president Marsha Roach works with stem cells, which require precise conditions. "We have an annual process of calibration and certification of our incubators and hoods," she says. "Our incubators are cleaned every six months with Wescodyne®, followed by an ethanol wipe using autoclaved wipes." Scientists at this company use autoclaved, deionized water in the water reservoir and water pan.

> "In addition to the air, dust, and samples that go into a CO_2 incubator, water can also cause contamination."

Roach and her colleagues also use careful techniques. "Plates of cells are never moved between incubators," she explains. "Only gloved hands washed with ethanol are allowed to enter an incubator to remove a plate or flask." Before daily use, they use Wescodyne followed by an ethanol wipe on their microscope stage, and the trays in their biological safety cabinets or laminar flow hoods. "This helps to ensure our plates or flasks are never put on a contaminated surface and then returned to the incubator," she says.

Most incubators will end up contaminated at some point. When that happens, Bates says, "run a high-temperature sterilization cycle that adheres to the U.S. Pharmacopeia standards for sterilization." Some scientists also opt for a copper interior, because it is germicidal.

No matter how much the technology has improved, it's still possible to make a mess of even the best CO_2 incubator and all the culture inside. With modern design and some careful use, however, scientists don't have to fight as much contamination as they once did.

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FOR ADDITIONAL RESOURCES ON CO_2 INCUBATORS, INCLUDING USEFUL ARTICLES AND A LIST OF MANUFACTURERS, VISIT WWW.LABMANAGER.COM/INCUBATORS

WHAT DO PIPETTE USERS HAVE TO SAY?

Pipettes can be found in almost every laboratory and, if you're looking to buy one, there are many options—manual or electronic, single or multi-channel. Luckily, a few main considerations can help in deciding whether or not to buy the latest pipette technology.

Types of pipettes used by survey respondents:

Manual: Single-channel	87%
Manual: Multi-channel	43%
Repeater	41%
Manual: Fixed volume	32%
Electronic: Single-channel	26%
Electronic: Multi-channel	18%
Electronic: Fixed volume	4%
Other	3%

Most common pipetting errors experienced by survey respondents:

Human errors	70%
Liquids stick to tip	45%
Viscosity reduces accuracy	43%
Surface tension reduces accuracy	34%
Pipettes take up more liquid	24%
Immersed tips carry over liquid	20%
Liquid temperature	16%
Liquids evaporate	11%
Other	7%

Nearly 62% of respondents are engaged in purchasing a new pipette. The reasons for these purchases are as follows:

Reviewing available options	38%
Plan to purchase in 12 + months	35%
Plan to purchase in 6 to 12 months	16%
Plan to purchase in the next 1 to 6 months	11%

TOP 5 QUESTIONS

You Should Ask When Buying a Pipette:

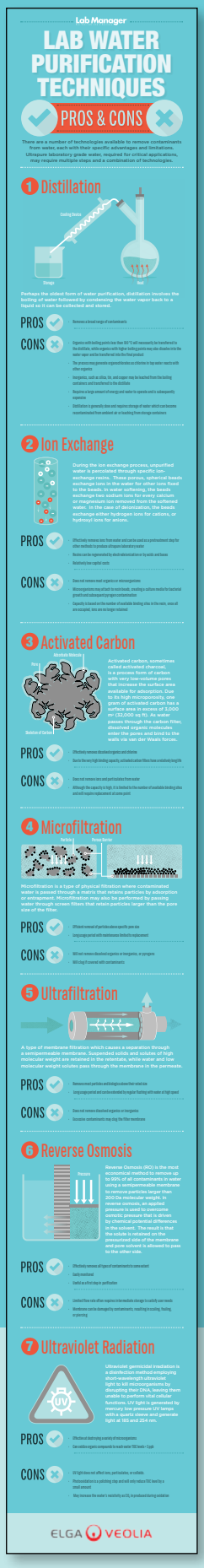
1. What differentiates the pipette from others offered in terms of performance and ergonomics?
2. Is the product compatible with other manufacturers' consumables (tips)?
3. What types of services are offered for this product? Calibration? Repair?
4. Does the company offer application support and technical phone support before and after product purchase?
5. What is the product life expectation? What is the product's warranty period? If the company discontinues the product, for how many years do they provide accessories and parts for the instrument?

TOP 10 FEATURES/FACTORS

Respondents Look for When Purchasing a Pipette:

CONSISTENT PERFORMANCE AND ACCURACY OF PRODUCT	94%
DURABILITY OF PRODUCT	82%
AVAILABILITY OF TIPS AND ACCESSORIES	70%
LOW MAINTENANCE / EASY TO CLEAN	67%
PRICE	63%
DESIGNED TO PERMIT RECALIBRATION	62%
ERGONOMIC OPERATION	46%
SERVICE AND SUPPORT	41%
WARRANTIES	37%
EASE OF ADJUSTMENT FOR VARIOUS VISCOUS LIQUIDS	35%

For more information on pipettes, including useful articles and a list of manufacturers, visit www.labmanager.com/pipettes



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BALANCES

EVEN A LITTLE AIRFLOW CAN THROW OFF A MEASUREMENT

by Mike May, PhD

Many scientific steps depend on accurately weighing a sample. How accurate a weight needs to be depends on many factors, including the application and even the amount of sample being used. When the accuracy really matters, even airflow can confound a measurement.

"Draft and vibration have the most significant effects on weighing quality," says Ian Ciesniewski, technical director for laboratory weighing technologies at METTLER TOLEDO (Columbus, OH). "The consequence of airflow is a deterioration in repeatability, which is the largest contributing component of measurement uncertainty—weighing error—in any laboratory weighing system."

Other features of a balance also come into play where airflow is concerned. "The influence of airflow depends on the readability of the balance," says Thomas Pertsch, senior product manager for premium lab balances at Sartorius (Goettingen, Germany). For a balance that can weigh 5–50 grams with a readability of 1 microgram, a draft can significantly influence the result.

Dealing with drafts

A balance must be placed in the right location. As Pertsch explains, that "means away from open windows and doors, and even away from people rushing by the balance." Also, balances should be placed on a heavy table, such as one with a stone top.

In most cases, a shield can keep airflow away from a sample, but not just any shield will do. Placing the shield in the path of an airflow can cool it, and that may influence the accuracy of weighing. For a balance that measures in increments of less than 0.1 milligram, the shield must be small enough to not be cooled by airflow, but large enough to block it.

Even a draft shield is not enough, especially for an analytical balance or a microbalance. "When the draft shield door is open—for example, when weighing-in a sample or placing a tare vessel or weigh boat or paper—the external air ingresses and can cause turbulence in the weigh chamber," Ciesniewski explains. Repeatability may suffer as a result.

Even with a great draft shield, a bad location will impact the results. "If there is a significant airflow in the weighing area, even a balance with a draft shield may be affected by the flow of air unsettling the body of the balance or draft shield, causing a vibration through the chassis of the balance," Ciesniewski says.

If a balance is used inside a hood, the need for blocking drafts can increase because of the higher air velocity. In these situations, it can be difficult to weigh even increments of 10 milligrams without some special method of handling airflow, says Pertsch.

Meet the needs

Price makes a difference in the accuracy of a balance. "Buy the best balance that you can acquire," says Ciesniewski. "High-end balances have better electronic filtering capabilities, and a more stable weight sensor, allowing the user to minimize the effects of the environment on the weighing result."

A great balance gets a scientist partway to good results, but the wrong environment can foul up the accuracy of even the world's best balance. In some cases, a little loss of accuracy in weighing doesn't matter that much. For instance, Laura Anderson, instructor and general chemistry lab coordinator at the University of South Florida in Tampa, says, "In the general chemistry labs, we don't have analytical balances, and with the normal balances we basically disregard the milligram difference that any airflow can cause." She adds, "Most of our labs are descriptive—qualitative rather than quantitative."

So, the level of air protection needed in weighing depends largely on the accuracy required. When the highest accuracy is needed, a balance must be in a suitable location with air flow managed as much as possible.

***Mike May** is a freelance writer and editor living in Texas. You may reach him at mike@techtyper.com.*

FOR ADDITIONAL RESOURCES ON BALANCES, INCLUDING USEFUL ARTICLES AND A LIST OF MANUFACTURERS, VISIT WWW.LABMANAGER.COM/BALANCES

GETTING A QUICK GRIND WITHOUT BREAKING THE BANK

by Erica Tennenhouse, PhD

A variety of tools are available to help researchers release the contents of their cells. Methods for cell disruption fall under two broad categories: mechanical methods, which use force to open the cell wall or lipid membrane, and nonmechanical methods, which include physical, chemical, and enzymatic methods. "I think that they both have merit," says Tim Hopkins, president and CEO of BioSpec Products (Bartlesville, OK), who notes that the vast majority of scientists favor mechanical methods because of their speed. Kyle James, vice president and business unit manager for Retsch at Verder Scientific USA (Newtown, PA), adds, "it depends on what type of sample you have…some cell types can be really difficult to break down so that's where we come into the mechanical side of it."

Scientists can disrupt their cells mechanically by grinding them with a simple mortar and pestle, sonicating them with an ultrasonic homogenizer, blending, freezing, or microwaving them. But, as Hopkins explains, more and more people are now turning to bead beating (aka bead milling). "It's really the only method that can lyse cells inside of a microvial by the addition of small glass beads, and essentially guarantee no cross contamination and guarantee that you don't have anything to clean up or decontaminate or make ready for the next sample," he says.

More options

Although bead mills have been around for some time, the products are still advancing. For the past 30 years, BioSpec has offered a series of bead mills that homogenize samples inside of 2 ml microvials, says Hopkins. More recently, the company has come out with a new bead mill called SoniBeast, which disrupts small samples around 10 times faster than their standard units do. In addition to Retsch's mixer mills, which have been on the market for over a decade, James notes that their CryoMill is highly popular among scientists. The unit connects to a liquid nitrogen tank to cool the material in the grinding jar to -196°C, resulting in a powder, rather than a liquid, matrix.

Accessories are also improving. "Whereas in the past we had only grinding jars or little 2 ml tube adaptors and things like that, now we're developing larger adaptors, so that customers have more options," says James. "Maybe you have more cell culture or more tissue than a 2 ml tube can fit; now we can offer additional accessories for larger sample sizes or higher throughput."

Quality and quantity

Still, scaling up—especially at an industrial scale—remains a challenge. One of the issues, explains Hopkins, is that mechanical methods of cell disruption generate heat. "So, the interest in scale-up often shifts to 'How can we control the heat? How can we get a throughput that is going to deliver a quality product and not cost a great deal of money with a very expensive piece of equipment?'" Though scaling up is a costly endeavor, in terms of price per sample, Hopkins says bead milling beats out almost all other methods.

A valuable resource

The vendors that sell these tools have, in many cases, developed in-depth knowledge of a wide range of cell-disruption methods for various sample types, making them a prime resource for their customers. "One day someone could be working with a biopsy sample…and you have other customers that are working with yeast cells, and other customers that are working with gram-negative bacteria," says James. "One thing that we want to do is make sure that we're recommending configurations and parameters to the customer." These recommendations are key, as they can mean the difference between releasing cell contents and destroying them.

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FOR ADDITIONAL RESOURCES ON MILLS AND GRINDERS, INCLUDING USEFUL ARTICLES AND A LIST OF MANUFACTURERS, VISIT WWW.LABMANAGER.COM/MILLS-GRINDERS

WHAT DO CENTRIFUGE USERS HAVE TO SAY?

When it comes to common technology in a laboratory, centrifuges rise toward the top of the list. Centrifuges separate particles and structures suspended in liquid by applying thousands of gravitational force equivalents to the sample through spinning and play a role in a wide range of workflows and applications.

Centrifuge rotor type(s) used by survey respondents:

Benchtop Centrifuge	66%
Microcentrifuge	54%
Benchtop Refrigerated Centrifuge	42%
Benchtop Clinical Centrifuge	23%
Floor Refrigerated Centrifuge	19%
Floor Ultracentrifuge	16%
Floor Centrifuge	14%
Benchtop Ultracentrifuge	10%
Other	5%

Centrifuge rotor type(s) used by survey respondents:

Swinging-bucket rotors	78%
Fixed angle rotors	70%
Vertical rotors	11%
Other	1%

Nearly 58% of respondents are engaged in purchasing a new centrifuge. The reasons for these purchases are as follows:

Replacement of aging system	52%
Addition to existing systems, increase capacity	26%
Other	7%
Require more speed (g-forces) and capacity	5%
Setting up a new lab	4%
Changing from the current type of centrifuge	4%
First time purchase	1%

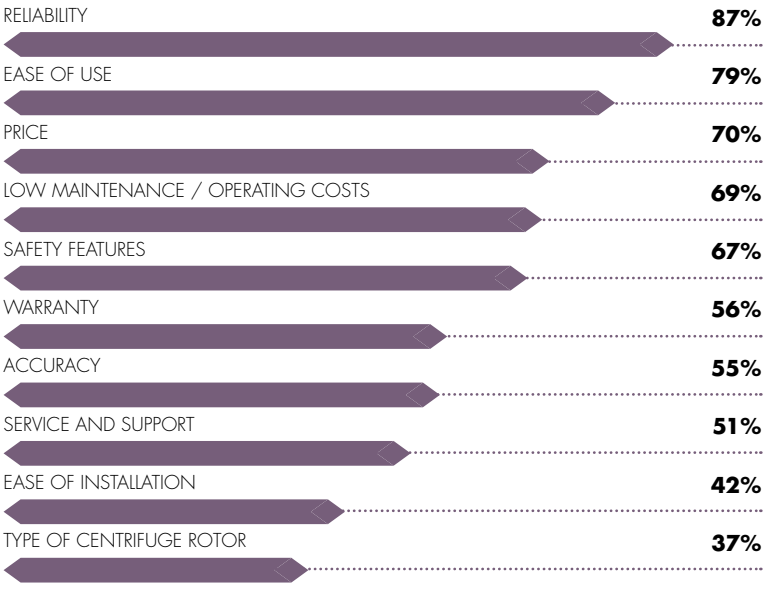
TOP 5 QUESTIONS

You Should Ask When Buying a Centrifuge:

1. What is the maximum g-force the centrifuge can generate?
2. How does the company's centrifuge differ from other ones that can achieve the same speed and capacity?
3. What kind of warranty comes with the centrifuge and what does it cover?
4. If the company discontinues the product, for how many years do they provide accessories and parts for the centrifuge?
5. Ask about the cost of the purchase—not just the price of the product being installed but the total cost of ownership including price, service expectations, warranty, etc.

TOP 10 FEATURES/FACTORS

Respondents Look for When Purchasing a Centrifuge:



For more information on centrifuges, including useful articles and a list of manufacturers, visit www.labmanager.com/centrifuges

WHAT DO STIRRER USERS HAVE TO SAY?

Magnetic stirrers are a popular type of laboratory stirrer that use a rotating magnetic field to cause a stirrer bar to rotate within the solution. These stirrers are often combined with a hotplate and are ideal for small volumes of non-viscous liquids and for situations in which a reaction must take place in a closed vessel or system. The overhead stirrer, however, is more suitable for larger volumes and more viscous solutions, but can be less convenient and more time-consuming to set up.

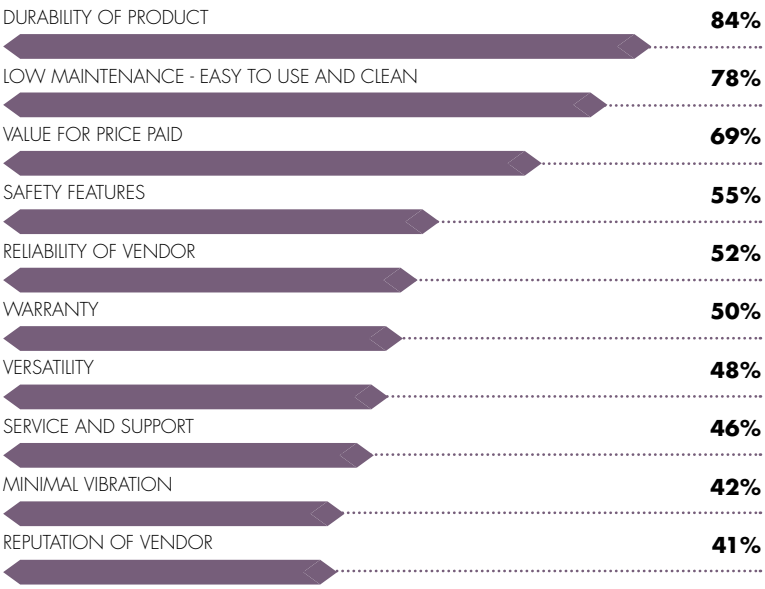
TOP 10 QUESTIONS

You Should Ask When Buying a Stirrer or Mixer:

1. What applications are you using the stirrer or mixer for? What result do you want to accomplish?
2. What are the maximum volume and the maximum viscosity that you can use the stirrer for?
3. Which stirring element is best suited to your application?
4. What are the features and specs of the stirrers or mixers available?
5. What level of accuracy does the digital speed indicator have?
6. What type of motor is used in the stirrer or mixer?
7. Can you determine the viscosity with the torque trend measurement?
8. Have you purchased everything you need to start mixing? Sometimes stirrers and mixers are sold as kits, while sometimes all or some of the accessories must be purchased separately.
9. Does the manufacturing company offer application and technical support over the phone?
10. What warranty and delivery options are available? How quickly will the new purchase arrive?

TOP 10 FEATURES/FACTORS

Respondents Look for When Purchasing a Stirrer:



Types of stirrer(s) used by survey respondents:

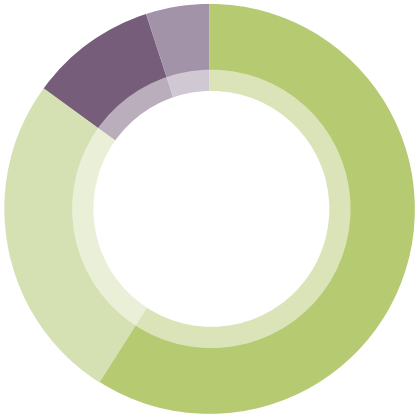
Hot Plate Stirrer	83%
Magnetic Stirrer	81%
Overhead Stirrer	26%
Other	9%

Stirrer problems reported by survey respondents:

Stirrer can't handle high viscosity fluids	45%
Stirrer can't handle large volumes	38%
Stirrer doesn't maintain speed	33%
Other	22%
Drive motor overheats	19%
Impeller frequently becomes jammed	12%

Nearly 58% of respondents are engaged in purchasing a new centrifuge. The reasons for these purchases are as follows:

Replacement of aging system	58%
Addition to existing systems, increase capacity	26%
Setting up a new lab	10%
Other	5%
First time purchase	0%



For more information on stirrers and mixers, including useful articles and a list of manufacturers, visit www.labmanager.com/stirrers-mixers

AN ACCELERATED PROCEDURE FOR THE DETERMINATION OF LIPIDS' OXIDATION STABILITY

Problem: **Every matrix containing lipids undergoes oxidation of the fat portion that causes, for example in food or feed samples, the loss of its natural sensorial qualities, bad smell, and unpleasant flavor.**

One of the main causes of deterioration of lipids is lipid autoxidation. The degree of lipid oxidation can be measured by chemical or physical methods; however, those are often time-consuming, expensive, and require high-skilled operators. Chemical methods that have been widely used include peroxide value, TBA test, carbonyl compound, Kreis test, and p-anisidine. In the case of physical methods, the most common are conjugated dienes content, infrared spectroscopy, refractive index, and headspace gas chromatography.

Another possible option for food samples is to store the products at 35°C and then monitor the oxidation markers during time on the extracted fat, or aldehydes content directly on the product. This, of course, could take several months to have enough data to decide if the product is suitable or not.

Solution: The solution to reduce the time of analysis that does not require highly trained personnel is to perform accelerated oxidation stability tests with the Oxitest Official Method (AOCS Cd 12c-16).

The VELP Oxitest reactor subjects the sample to a high oxidative stress environment in order to evaluate, in a short period of time, the resistance to fat oxidation. The main innovation introduced by the Oxitest is the opportunity to work directly on the sample as it is (liquid, solid, or pasty), avoiding the critical use of chemicals for the extraction of the lipid.

This property makes it ideal for an easy quality control on both food raw materials and finished foods and guarantees representative results. In fact, other components of a product like chemical oxidants or transition metal can promote oxidation and the use of extracted matter may not be a suitable predictor of stability.

The Oxitest measures the absolute pressure change inside the two chambers, monitoring the oxygen uptake of the active components of the samples, and automatically generates a value expressed in time, called the Induction Period (IP). The longer the IP, the more resistant a sample is to lipid oxidation over time.

The instrument features two temperature regulated and hermetically sealed titanium chambers in which oxygen is purged until the pressure within both chambers is at the desired level (usually 6 bars). The temperature is then set, commonly at 90°C, in order to create the conditions to accelerate the oxidation process.

The Oxitest reactor is entirely controlled via PC through the intuitive OXISoft™ software. The information provided by the Oxitest method is crucial for shelf life study of products. The OXISoft™ manages all the analysis steps and easily provides valuable data to enable researchers to:

- Estimate shelf-life by testing the sample at different temperatures (80-90-100°C) and elaborating an experimental curve that predicts the behavior at room temperature;
- Study oxidation at different storage time intervals;
- Evaluate the adequacy of storage conditions;
- Evaluate the best packaging solution;
- Compare the oxidative stability of different formulas for food preparations;
- Evaluate the oxidative stability of vegetable oils of different botanical origin, different age, or different storage conditions;
- Evaluate the effectiveness of antioxidants;
- Control the quality of incoming raw materials and outgoing finished products.

Several preinstalled methods can help to easily identify the most suitable working conditions. Furthermore, the software allows a comprehensive reporting tool and data export.

In conclusion, the stability tests, performed with the Oxitest reactor, accelerate the oxidation process that under normal conditions may need weeks or months and provide fast, accurate, and reproducible results without using solvents or chemical reagents.

For more information, visit www.velp.com

▲*Oxitest is able to perform an oxidation stability test directly on the sample as it is (solid, liquid, or doughy) with no need for a preliminary fat extraction.*

NEW AUTOMATION FRIENDLY RESERVOIRS SAVE REAGENTS AND REDUCE PLASTIC WASTE

INTEGRA has expanded its Clear Advantage™ product family to include automation friendly reagent reservoirs designed to save reagents and reduce waste while simplifying pipetting activities. The new reagent reservoirs – available in 150 and 300 ml volumes – offer the lowest possible dead volumes, and are compatible with INTEGRA's VIAFLO 96/384 hand-held electronic multichannel pipettes, as well as other liquid handling platforms. The Clear Advantage design also gives scientists a clear view of the tips during pipetting operations, helping to ensure the best liquid handling results.

As automation becomes more and more important, the design of labware consumables, such as reagent reservoirs, becomes increasingly important. Reagent reservoirs offer a convenient solution for the temporary storage of liquids during pipetting applications, but it is essential that they are carefully designed and manufactured to ensure smooth automation of liquid handling processes and minimize wastage of reagents. The use of automation friendly ANSI/SLAS-formats also helps to extend walkaway time by simplifying logistics and allowing robotic grippers to move the reservoirs.

INTEGRA's Clear Advantage™ product family is designed to enable scientists to benefit from walkaway automation while saving reagents and reducing plastic waste. The company's recently launched automation friendly reagent reservoirs combine the lowest possible dead volumes – saving on reagents – with reduced plastic waste to offer a more application and environmentally friendly solution for automated liquid handling. The system consists of disposable, virgin polystyrene inserts that fit into reusable, ANSI/SLAS-format bases with clearly visible volume markings. Users simply choose between 150 or 300 ml reservoir inserts, which can be replaced as required, saving both precious lab space and money.

Each flat bottom insert benefits from INTEGRA's revolutionary SureFlo™ anti-sealing array, which prevents pipette tips from sealing off and stops liquid from 'popping' into tips, filters or the pipetting head. A specially formulated surface treatment avoids pooling of liquids, resulting in a dead volume of less than 3 ml. For ease of use, the reservoirs feature clearly visible integrated volume graduations, allowing rapid, accurate filling with the required reagent volume. Unused reagent can be conveniently returned to the source container via the pour back spouts, or a latching lid can be attached to the reservoir, enabling short-term storage while preventing evaporation and spillage. Unique dual viewing windows ensure optimal positioning of the pipette tips, and a space-saving, stackable design significantly reduces storage requirements.

The inserts are available in two volumes – 150 and 300 ml – in either individually sealed or bulk packaged options, and are compatible with INTEGRA's VIAFLO 96/384 hand-held electronic multichannel pipettes, as well as other liquid handling platforms.

Visit www.integra-biosciences.com to request your free trial pack or to watch the product video.

INTEGRA

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Asynt www.asynt.com

Laser Diode Module System

GPL Series

- Intended for education, light assembly, simple alignment, positioning, and levelling jobs
- Includes a 1/2" OD NPT threaded housing with mounting hardware and plug-in USB type power supply
- Cable length is 36" and available patterns include green or red dot, or green or red line, with a nominal focal length of 17"

BEA Lasers www.bealasers.com

Metal-Housed Heating Mantles

HM

- For use in research and development labs that employ round-bottom flasks for heating liquids
- Provide exceptionally consistent, easy-to-control heat
- Fit flasks with capacities between 50ml and 6,000ml and provide high-temperature capabilities up to 450°C (842°F)
- Offered in tabletop designs and are available with built-in controllers
- Are thermally insulated for safe touch and grounded for added safety

BriskHeat www.briskheat.com

Pocket Testers

Oakton®

- These new and improved pocket testers stand up to everyday use, harsh environments, and time
- Stand upright with a new cap design that is versatile, functional, and leakproof
- Feature an easy-to-replace sensor module and a dependable double-junction pH electrode sensor
- Testers including the new features are: pHTestr® 50, pHTestr® 50S Spear-Tip, ORPTestr® 50, CTSTestr™ 50, and PCTSTestr™ 50 Multiparameter

Cole-Parmer ColeParmer.com

Data Loggers with Wireless Technology

Digi-Sense

- Now available with TraceableLIVE wireless technology, allowing workers to stay connected to their environment 24/7
- TraceableLIVE is ideal for those who want to monitor critical environments and get alerts wherever they go
- Provide a simple, efficient, and reliable way to ensure critical samples are not compromised due to parameter variations

Cole-Parmer ColeParmer.com

Particle Analyzer

FlowCam® Nano

- Provides digital images of particles ranging in size from 300 nm to 30 µm
- Automatically reveals protein agglomerates, silicon oil droplets, glass shards, and other opaque, transparent, and translucent sub-visible particles with the high resolution imagery needed for identification
- May serve as an invaluable companion to USP<788> compliance testing methods for particulate matter

Fluid Imaging Technologies www.fluidimaging.com

Pump Head

Masterflex® L/S® Cytoflow™

- Developed specifically for pumping live cells and shear-sensitive fluids
- Ideal for use in biopharm and microbiology applications and performance in live-cell applications has been verified by independent test data
- Features a large-diameter rotor resulting in high flow rates at low motor speeds
- Available in 2- and 3-roller configurations

Cole-Parmer ColeParmer.com

Horizontal Gel Electrophoresis Units

- Consist of 12 different sizes with a large selection of combs and other accessories
- Provide higher reproducibility and speed with active cooling for larger gel sizes
- Designed to allow more samples to be run using less buffer and agarose
- Feature in-unit and external gel casting
- Specialty units for high throughput applications are offered

Hoefer www.hoeferinc.com

Ultrasonic Flow Sensors

Masterflex®

- Accurately and noninvasively measure the flow rate of liquid in tubing used with peristaltic pumps
- The ultrasonic sensor never contacts the working fluid, making it reusable in single-use applications and yielding significant recurring savings over disposable sensors
- An optional communications package allows users to adapt the flow sensor to their specific application, and also monitor and record data

Cole-Parmer ColeParmer.com

Reference Ellipsometer

UVISEL Plus

- Includes the newest acquisition technology—FastAcq— designed to measure thin film samples faster, and more accurately than ever
- FastAcq technology enables a sample measurement from 190 to 2100nm to be completed within 3 minutes, at high resolution
- Introduces a new calibration procedure, delivering faster performance and accuracy
- Offers microspots for patterned samples down to 50µm

HORIBA Scientific www.horiba.com/uviselplus

Compact Vortex Flow Meter

LIQUI-VIEW *Base*

- Now equipped with a bright, wide-angle, and easy-to-read display for local readout purposes
- Besides a local readout, these models also offer 4-20 mA output signals
- Can be mounted in any position and can be supplied in full scale ranges from 10 l/min up to 150 l/min at max, 12 bar pressure rating

Mass Flow ONLINE www.massflow-online.com

Screw Cap Recappers

Univo SR006 & SR004

- Provide a cost-effective solution to recap 48-well and 24-well format sample storage tubes securely and uniformly
- Offer users the ability to cap a row of 6 or 4 tubes in 5 seconds and a whole rack of 48 or 24 tubes in less than 1 minute
- Help minimize sample evaporation and improve throughput

Micronic www.micronic.com

PRODUCT SPOTLIGHT

ULTRA-COMPACT AND ULTRAPURE

NEW SYSTEM OFFERED FOR LABORATORIES NEEDING LOW VOLUMES OF ULTRAPURE WATER

Those who don't have much space in their labs but need low volumes of ultrapure water have a new option with the recent release of Sartorius' arium® mini. This especially compact ultrapure water system delivers a flow rate of one liter per minute and is specially designed for ultrapure water requirements of less than 10 liters per day. This system is also only 28 cm (11 inches) wide, meaning it can fit in almost any lab.

Feed water needed to produce ultrapure water is supplied by the 5-liter bag integrated on the side of the system. Originally developed for the pharmaceutical industry, this bag is optimal for storing purified water. The closed bagtank system prevents secondary contamination while ensuring consistent long-term water quality. Uncomplicated exchange of the bag also facilitates upkeep of the system and considerably reduces maintenance time compared with conventional tank systems. The bagtank does not require any hazardous cleaning chemicals, further increasing user safety as a result.

Besides its unique bagtank technology, the system is equipped with a high-resolution, touch-activated color display. Easy-to-understand icons guide the user intuitively through the menu. The Favorites function automatically stores the volume of ultrapure water last dispensed. This prevents errors during repeated dispensing of identical volumes, helping to increase the reliability and efficiency of lab work procedures.

Users can choose between two model versions to suit their individual requirements—the standard version, which is independent of a permanently installed water tap—and the arium® mini Plus, which can be directly connected to a feed water tap.

For more information, please visit www.sartorius.com

High-Throughput Water Purification System

Milli-Q® HR 7000 Series

- Offers laboratories and research facilities a high-throughput water purification system as a uniquely connected and sustainable central pure water solution
- Ensures constant water quality and flow rate, while reducing water consumption and running costs compared to other high-throughput reverse osmosis (RO) systems
- Can reliably produce from a few hundred to up to 13,000 liters of pure water daily

MilliporeSigma goo.gl/yjPmMU

Wireless Flow Totalizer

- Connects to industry-standard inductive turbine flow meters to measure, locally display, wirelessly transmit, and archive flow measurements
- Data and diagnostics are available locally using the display as well as remotely from a SignalFire Gateway using Modbus standard protocol
- Maintains an internal 30-day log of daily flow totals for historical analysis or backup storage

SignalFire Wireless Telemetry www.signal-fire.com

Cryo-DualBeam Microscope System

Aquilos

- The first commercial cryo-DualBeam (focused ion beam/scanning electron microscope) system dedicated to the preparation of frozen, thin lamella samples from biological specimens for high-resolution tomographic imaging in a cryo-transmission electron microscope
- Allows customers to reliably create the samples with precisely-controlled thickness with minimal investment in time and effort

Thermo Fisher Scientific www.thermofisher.com

Field Emission ESEM

Quattro

- This field-emission environmental scanning electron microscope (ESEM) is designed for versatility
- Enables scientists to perform high-resolution imaging and analysis of most material types under a wide range of experimental conditions, including: hot, wet, or chemically active
- The Quattro's environmental capability allows scientists to study materials in a range of environments as they develop new materials and products across disciplines

Thermo Fisher Scientific www.thermofisher.com

Scanning Transmission Electron Microscope

Talos F200i

- Can be customized to meet users' imaging and analytical requirements
- The automation of the F200i system is designed to ensure high productivity and fast, easy switching among users
- Easy mode switching and constant power lenses increase productivity by permitting fast changes among imaging and analytical modes, without waiting for the system to equilibrate

Thermo Fisher Scientific www.thermofisher.com

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- Designed to minimize energy usage and noise, while maintaining high levels of performance and maximizing storage capacity
- Are the only current lab-grade undercounter refrigerators using thermoelectric devices in place of compressor technology for variable speed control
- Provide whisper-quiet operation at just 35 dBA
- Consume up to 37 percent less energy than other models

Thermo Fisher Scientific www.thermofisher.com

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FlowLab Column™

- Designed for heterogeneous catalysis applications
- Offers the potential to replace conventional stirred batch reactors for continuous, heterogeneously catalyzed liquid phase reactions
- Features a HotCoil™ heated reactor module fitted with a HotColumn adapter to enable operation up to +260°C (300°C as an option)
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Uniqsis goo.gl/JCYCKz

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- Provides both flame-resistant (FR) properties and chemical-splash protection (CP)
- Combine the FR protection of Nomex® IIIA fabric with Westex ShieldCXP™, a proprietary chemical-splash protective technology
- FR/CP line also includes lab coat styles for both men and women
- Suited for work environments where both thermal hazards and liquid chemicals are present

Workrite Uniform Company www.workritefrcp.com

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- Complement ZEISS's current portfolio of high-speed USB 3.0 microscope cameras
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- Feature high-speed USB 3.0 connections and active thermoelectric cooling

ZEISS www.zeiss.com

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MagMAX™ CORE

- This magnetic bead-based sample preparation kit for diagnostic laboratories can be used with the widest range of diagnostic samples
- Consists of a robust core chemistry that couples easily with modules to increase flexibility in choice of diagnostic samples
- Has built a sample preparation process that extracts very high quality nucleic acids

Thermo Fisher Scientific thermofisher.com/animalhealth

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Vector Laboratories vectorlabs.com

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- Safely and accurately automates the most dangerous step of sample prep for metals digestion—the addition of acids and reagents
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- A five-way valve eliminates the need to swap out reagent bottles when switching digestion methods, providing easy switching between reagents

Environmental Express EnvExp.com

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- Designed to overcome the multiple inconsistent elements in standard water bath thawing practice, the series delivers a simple, reproducible, and traceable recovery system that maintains cell viability to prevent loss of therapeutic effect

GE Healthcare Life Sciences asymptote.co.uk/viathaw

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ARUP Laboratories www.aruplab.com
IDbyDNA www.idbydna.com

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- Enables targeted RNA expression analysis and has the flexibility to capture and analyze hundreds to tens of thousands of individual cells in a broad range of sizes and types
- The system's specific gene panel approach can help generate similar results as a whole transcriptome analysis assay at a fraction of time and cost

BD bd.com/Rhapsody

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Beckman Coulter Life Sciences www.beckman.com

Solid Phase Extraction Plates

EVOLUTE® HYDRO

- Include an integral hydrolysis capability that enables chemists to perform sample hydrolysis within the extraction plate; saving time and reducing sample transfer issues
- Packed with high quality 30 µm EVOLUTE® media, with CX (mixed mode strong cation exchange) and ABN (wettable/non-polar) phases available at launch
- Can be processed using 96-well compatible positive pressure manifolds, vacuum manifolds, and automated liquid handling systems

Biotage www.biotage.com

C. difficile Assay

Simplexa® C. difficile Direct Assay

- Recently received clearance from the U.S. Food and Drug Administration
- Runs on DiaSorin Molecular's LIAISON® MDX qPCR system, a scalable benchtop instrument that delivers qualitative and quantitative, sample-to-answer, multi-analyte results
- Detects the Clostridium difficile toxin B gene (tcdB), present in liquid or unformed stool samples, aiding in the diagnosis of C. difficile infection

DiaSorin Molecular goo.gl/NPR37J

Parvovirus Antigens

- Now include eight new recombinant antigens to Binding Site's offering of products for in-vitro diagnostic (IVD) manufacturing and research applications
- The recombinant Parvovirus NS1; Parvovirus VP1; Parvovirus VP2; Parvovirus VP2-VLP; Parvovirus PepA (VP1 unique); Parvovirus PepB (VP2 C-term); Parvovirus PepC (VP1 N-term); and Parvovirus PepD (VP1 C-term) have all been expressly designed for use as an integral component within solid phase enzyme immunoassay (EIA) test procedures, including ELISA

Binding Site www.immunologicals.com

Dendritic Cell Maturation CDM

PRIME-XV®

- A chemically-defined, animal component-free medium for the differentiation of monocytes into immature dendritic cells, and subsequent maturation in dendritic cells
- Provides a robust method for the generation of Mo-DCs in chemically-defined culture conditions, thereby maintaining their capacity to induce T cell response
- The ideal complement to PRIME-XV T Cell CDM, the first commercially available chemically-defined medium for T cell culture

Irvine Scientific www.irvinesci.com

Live Cell Imaging System

CytoSMART™ 2

- Features an advanced optical system and more powerful camera unit, which enables researchers to capture higher-resolution images of their cell cultures
- Allows images to be digitally enlarged two-fold to display more cellular detail for enhanced monitoring of cell cultures, migration assays, and differentiation experiments
- Easy to set up and can take time-lapse recordings without having to remove cultures from the incubator

Lonza www.lonza.com/cytosmart

2D Optical In Vivo Imaging Systems

IVIS® Lumina™ S5 and X5

- Provide high-sensitivity, high-throughput bioluminescence, and fluorescence imaging with spectral un-mixing
- Include a camera with an expanded field of view; scientists can capture more subjects simultaneously
- Offer high throughput and high resolution X-ray imaging
- The multimodal IVIS Lumina X5 integrates high-resolution X-ray imaging, allowing scientists to explore multiple facets of a disease

PerkinElmer www.perkinelmer.com/invivo

Multimode Plate Reader

VICTOR® Nivo™

- Designed to fit almost any lab space
- Instrument provides high performance detection modes and easy-to-use software, which allows scientists to be able to accelerate biochemical and cell-based assays for disease research and drug development
- Features a wide range of key detection modes, top and bottom reading for all modes, and space for up to 32 filters

PerkinElmer www.perkinelmer.com/Nivo

Gel and Blot Imaging System

G:BOX mini

- This compact, upgradeable, multi-application system is suited for all types of gel and Western blot imaging
- Features a motorized stage, high performance camera, and the option to add HI-LED lighting
- With its high performance 0.95 lens, 6 or 9-megapixel camera, this system can image and resolve close bands or spots even on complex 2D gels

Syngene www.syngene.com/gbox-mini

Lentiviral Production System

Gibco™ LV-MAX™

- The first optimized system that provides a scalable and high-yield lentiviral vector (LVV) production platform
- Based on a high-density suspension culture of HEK 293-derived viral production cells in chemically defined, serum-free, and protein-free LV-MAX production medium
- Enables lentiviral production from a 96 deep-well plate to a 2 L bioreactor

Thermo Fisher Scientific www.thermoscientific.com/lentiviral

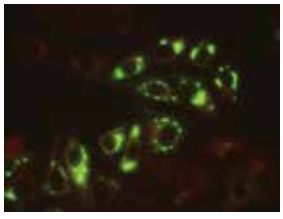
Solution for Drug Implant Production

Pharma *mini* implant line

- The first commercially available, fully-integrated solution for polymer-based drug implant development and production using hot melt extrusion (HME)
- Provides pharmaceutical manufacturers with a complete end-to-end manufacturing line from a single supplier
- Built around the Thermo Scientific Pharma mini HME twin-screw micro compounder
- Incorporates a range of components in an innovative configuration

Thermo Fisher Scientific www.thermofisher.com/implantline

Yellow Fever Monoclonal Antibodies



- New set of monoclonal antibodies to the NS1 protein of the virus now available from ViroStat
- Protein appears early during the infection in serum of those infected
- Do not cross react with related Flaviviruses
- ELISA pairing recommendations can be found on the data sheet which can be downloaded from the website below

ViroStat www.virostat-inc.com

ASK LINDA

ADVANCING YOUR CAREER

QUESTION:

Dear Linda,

I have been managing the same lab for nearly 10 years. While I enjoy the work, the company I work for, and my staff and colleagues, I am beginning to think about taking the next step on my career path. There are opportunities to move up in my organization, but I'm not sure how best to proceed. Can you offer up any suggestions for how to best prepare for a higher level position within the company?

Thanks,

Denise

HAVE A QUESTION FOR LINDA?

EMAIL HER AT: *LINDA@labmanager.com*

ANSWER:

Dear Denise,

While there are specific skills needed to be an effective manager, there are also mental attitudes or mindsets that aspiring managers need to develop. Specific proficiencies such as oral communication and time management skills are not enough without cultivating these broader mindsets, which require that you:

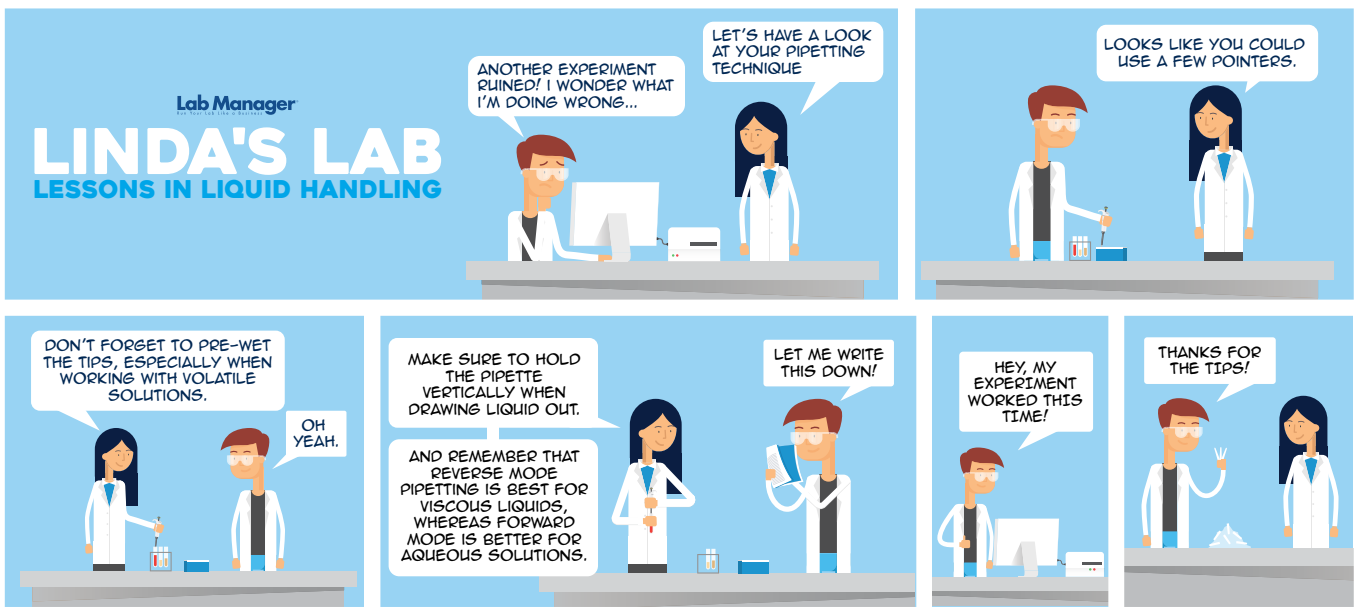
- Develop an external focus beyond your company to include your industry, your suppliers, and your customers. This is necessary to identify business opportunities and competitive challenges.
- Adopt a commercial mindset. You need to be involved in identifying commercial opportunities and working back from these opportunities to develop and prioritize laboratory activities that deliver value. This means understanding how your employer makes money within and across its businesses.
- Deliver results by motivating people to succeed, tracking performance, and rewarding success.
- Provide speed in all of the above by making effective decisions in a timely manner, removing barriers to timely action, and managing risk.
- Strive for simplicity by eliminating activities that add unnecessary costs and do not deliver commercial value.

Your challenge for moving up the career ladder is not about implementing new techniques, business practices, or technology, but in understanding your role in the larger business enterprise.

Good luck.

Cheers,

Linda



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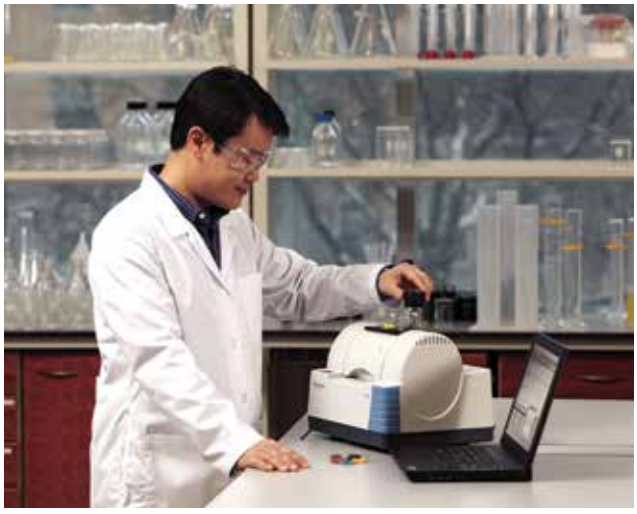

You have no time to second guess if your answers from routine analyses are correct. Especially when your customer is waiting for you to release products for an overnight shipment. Fast, accurate identification of product quality is crucial for PASS/FAIL decisions whether you are in the lab, in the raw material warehouse or on the production floor. Depend on the **Thermo Scientific™ Nicolet™ iS5 FTIR Spectrometer** to go anywhere you need definitive answers.

Don't risk bad QC results with unproven spectrometers.

The Nicolet iS5 FTIR spectrometer delivers:

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Worry-free maintenance – extended warranties come standard and user-accessible parts minimize service costs and downtime

Multi-user rugged design - Magnesium-alloy construction provides stable thermal properties, vibrational dampening and reduced weight

More options, more capabilities- unlike other FTIR spectrometers, the Nicolet iS5 spectrometer accepts most commercially available FTIR accessories (e.g., diamond ATR, microsampling, liquid transmission, etc.)

High-sensitivity reveals contaminants – high signal-to-noise ratios identify even the smallest contaminant spectral peaks

Reproducible push-button simplicity – rely on simple operation that helps your multi-user lab manage increasing workloads

Answers that go anywhere – the compact, light-weight design means you can take the Nicolet iS5 spectrometer from the lab to the manufacturing plant with ease

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- Contaminant analysis
- Chemical profiling/fingerprinting

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d. Percent Paid and/or Requested Circulation (Both Print & Electronic Copies) (16b divided by 16c × 100)	98%	99.6%

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LAB MANAGER ONLINE

We look back at our web content since the October issue and look forward to what's in store for the upcoming December issue.

1 Five Awesome Fall Science Experiments

With fall well underway, we thought we'd share some of the coolest Autumn-related science experiments from around the Web that you can do at home with friends and family. While many activities are simply classic home-based science experiments with the addition of pumpkins or apples, others help add to our understanding of the changing seasons.

Read more at **LabManager.com/fall-experiments**

2 Trending on Social Media: Common Misconceptions About Used Lab Equipment

As of October 16th, *Lab Manager*'s top October issue article posted to social media was our Business Management piece on preowned laboratory equipment. This article covered the key misconceptions many people have about used lab equipment and what purchasers should look for when considering second-hand products.

Read more at **LabManager.com/buying-preowned**

3 Most Popular Webinar

Last month's top webinar on LabManager.com with 413 registrants was "Conflict Resolution in the Lab: Big and Little Conflicts," presented by Scott D. Hanton, PhD. This webinar shared how to use positive conflict to resolve issues in the workplace. Though it ran on Sept. 27, you can still catch it on demand at the link below.

Read more at **LabManager.com/conflict**

LabManager.com

NEXT ISSUE ➡

The Right Way to Automate Your Lab

Just as Henry Ford applied automation to car manufacturing and the McDonald brothers introduced automation to fast food, laboratory science is currently undergoing its own automation revolution. And just as it did for the car and fast food industries in the past, this push towards automation is changing the way laboratories do business.

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Research samples are much too valuable to rely on decades-old, compressor-based cooling technology that's expected to fail.

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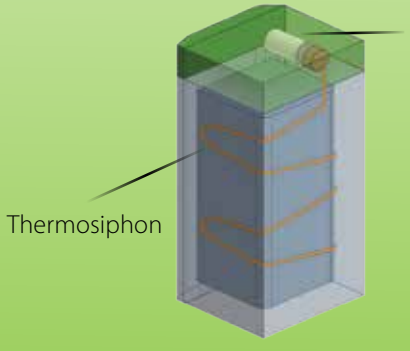

The free-piston Stirling engine's advanced integral linear motor system has only two moving parts and uses a gravity-driven thermosiphon to cool the cabinet interior.

Visit **NoCompressors.com** to learn how this is all made possible with our revolutionary Stirling Engine.

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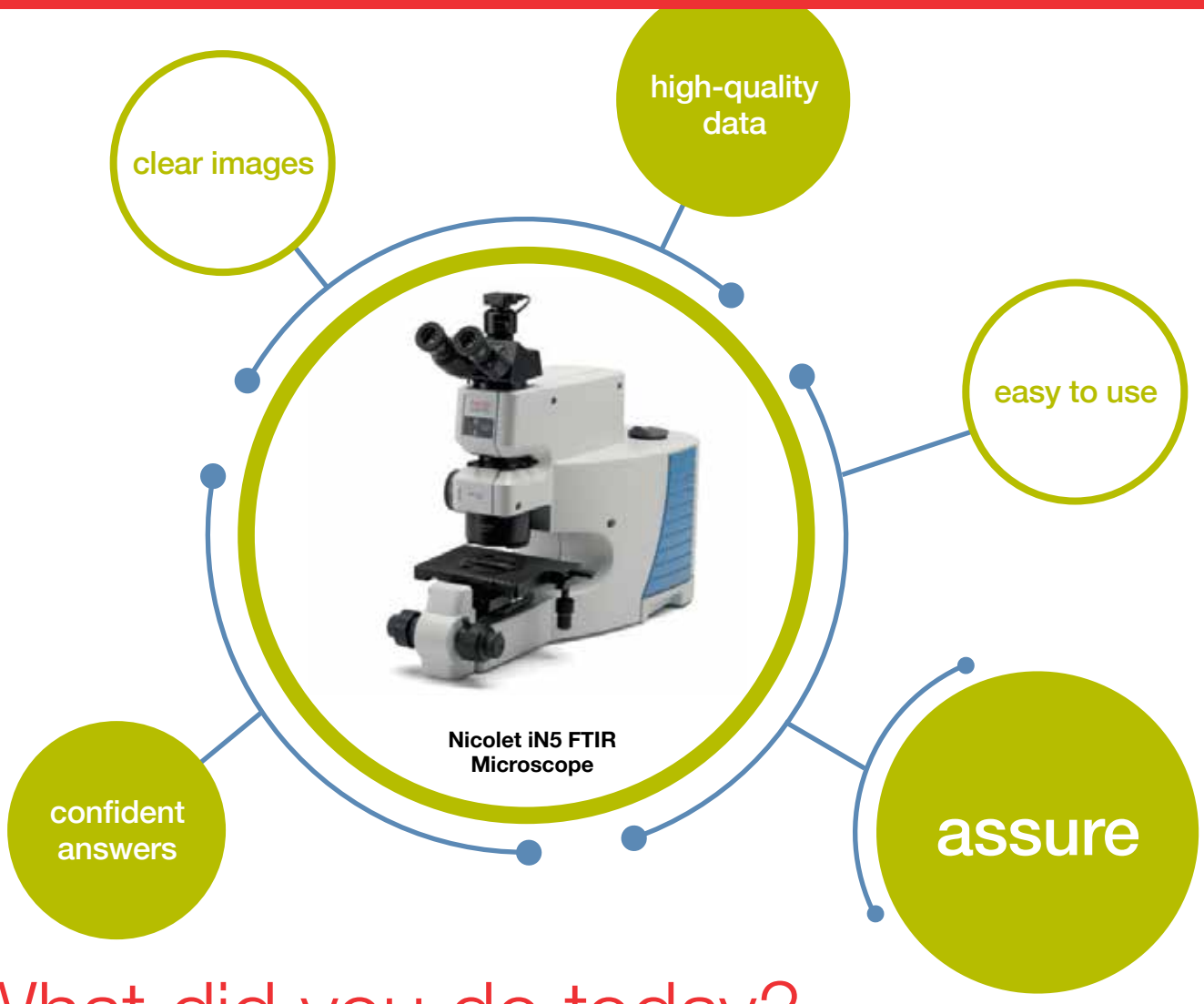

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