



**Viewpoints**  
page 2

**Monitoring of Residual  
Impurities Encountered  
In Bioprocessing**  
page 3

**Lancaster Labs offers  
Melamine testing**  
page 4

**Lancaster Labs hosts Asahi  
Planova Training Seminar**  
page 5

**Cell Bank Manufacturing  
Suites and Storage  
capabilities added**  
page 6

**People are the chemistry**  
page 7

**Pharmaceutical  
NEWS**

Fall 2009

# Our People, Your Place



by J. Wilson Hershey, Ph.D., President

In today's cost-conscious environment, everyone is being required to do more with less. This is most evident in the employee headcount reductions and restrictions that many companies face. Using temporary workers is one of the few ways that organizations can meet their business objectives while still controlling costs, but this solution comes with a number of challenges. Temporary workers can be considered co-employed and have to be managed in specific ways to avoid having them be viewed as employees from a legal standpoint.

One way that firms handle this risk is to limit the amount of time that a temporary worker is allowed to remain in a position. Typically, after 12 months, even the best temps need to be replaced to avoid the pitfall of having them viewed as an employee. So after you spend months training someone, they have to leave, and you get to do it again, wasting valuable time and money. And knowing that their days are numbered, temporary workers frequently start looking for other opportunities on their own before their contract expires.

Legal issues present an even more perilous problem than turnover. What criteria determine a worker's status and how can you avoid the liabilities related to co-employment? The IRS has posed a series of questions that can help you decide if your company is at risk for co-employment complications. Known as the 20 Factor Test (see sidebar), the questions evaluate how much control the company has over a worker, and companies need to

tread carefully to ensure their employment of temporary workers meet all the criteria.

At Lancaster Laboratories, we have a unique solution to your need for additional staff that protects you against the pitfalls of hiring temps. Our Professional Scientific Staffing<sup>sm</sup> has been specifically designed to provide a "non-permanent" workforce for one or more years with no worries about co-employment issues. We recruit, hire, train and manage these scientists, who work in your facility. They are Lancaster Laboratories employees, with all the benefits that our in-house, full-time employees enjoy. We've structured our program so the employment relationship is clear and consistent with the IRS 20 Factor guidance. In fact, we're so certain that our model meets the co-employment test that we'll guarantee it in our contract.

We've successfully implemented Professional Scientific Staffing<sup>sm</sup> programs at client facilities from California to Massachusetts and even in the EU, as clients have begun to see the advantages of having their scientific staff selected and managed by a company that has nearly 50 years of experience delivering laboratory services. Our proven track record in human resources best practices and the fact that Professional Scientific Staffing<sup>sm</sup> scientists are full-time employees of Lancaster Laboratories results in the highest quality staff and turnover rates that are dramatically lower than with traditional temporary employees. Our workers in your facility can cost you less than your own full-time employees, while providing a variable cost resource. We've been able to prove this by measuring productivity, turnaround time, quality, turnover and safety at Professional Scientific Staffing<sup>sm</sup> sites.

If you have the workload, but not the workforce, our Professional Scientific Staffing<sup>sm</sup> program can help increase capacity quickly without adding to fixed headcount. And our unique model has allowed us to help clients meet other resource challenges, too. Take the trend that's emerging in some industries to focus on the core business and outsource any segments that aren't directly related to that. Obviously, samples can be sent to Lancaster Laboratories' facilities if an organization decides that laboratory testing isn't germane to their core

business, but there may be other considerations that aren't met by traditional outsourcing. These include tight turnaround times, ability to work under your own quality systems and reluctance to share proprietary information with people outside the company. We've been able to address these needs by placing our scientists in client facilities.

For years, Lancaster Laboratories has used the tag line, "People Are The Chemistry" and nowhere is this more evident than our Professional Scientific Staffing<sup>sm</sup> program, where our highly motivated, efficient, well-trained scientists work solely on your projects at your location as trusted partners in achieving your company goals.

## 20 Factor Test

1. Instructions
2. Training
3. Integration
4. Services Rendered Personally
5. Hiring, Supervising, Paying Assistants
6. Continuing Relationship
7. Set Hours of Work
8. Full Time Required
9. Doing Work on Employer's Premises
10. Order of Sequence Set
11. Oral or Written Reports
12. Payment by Hour, Week, Month
13. Payment of Business and/or Traveling Expenses
14. Furnishing of Tools and Materials
15. Significant Investment
16. Realization of Profit or Loss
17. Working for More than One Firm at a Time
18. Making Service Available to General Public
19. Right to Discharge
20. Right to Terminate

# Monitoring of Residual Impurities Encountered In Bioprocessing

by Dr. Jon S. Kauffman, director of Biopharmaceutical Services and Analytical Method Development & Validation

Profiling of impurities in biopharmaceutical products is a regulatory expectation. Since residuals are typically present at low levels in difficult sample matrices, development and qualification of assays can be quite challenging. Matrix types can vary greatly due to the fact that sampling at a variety of steps is required to accurately confirm clearance throughout the production process.

Some residual impurities are introduced in the upstream steps as essential ingredients of the fermentation or cell-culture media. Various impurities result from the culture growth and harvest. Nucleic Acids such as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) and Host Cell Proteins (HCPs) are some of the unwanted cell components that accompany the protein of interest after cell lysis. Antibiotics are added to the cell-culture media to control bacterial contamination. Common antibiotics used include kanamycin, ampicillin, penicillin, amphotericin B, tetracycline, gentamicin sulfate, hygromycin B and plasmocin to control mycoplasma.

Additional residual impurities are introduced throughout the process. Process-enhancing agents and catalysts are added to make some of the steps more efficient and increase yield of the product. Guanidine and urea are added for solubilization of the fermentation output. Glutathione and dithiothreitol (DTT) are used during reduction and refolding of proteins and Isopropyl  $\beta$ -D-1-thiogalactopyranoside (IPTG) is used to induce gene expression and to aid in the refold process.

Finally, there are other residual impurities introduced to aid in the purification of the product downstream. Chromatographic purification of target proteins may require the use of alcohols and glycols, which must be cleared from the process. Surfactants are added to aid

in separating the protein, peptide and nucleic acids from the process stream. Examples include Triton-X, Pluronic, Antifoam- A, B, C, Tween or Polysorbate.

The variety of residual impurities requires the employment of a wide array of analytical techniques to characterize and quantify residuals. Lancaster Laboratories has added capacity to the following areas.

**Mass spectrometry (MS)** yields both qualitative and quantitative information and is one of the primary tools for monitoring and identifying residual impurities. Residual antibiotics can be measured accurately at part-per-billion (ppb) levels using LC/MS/MS in very complex sample matrices.

**High Performance Liquid Chromatography (HPLC)** is a common method of separation and can be configured with various detectors, including ultraviolet (UV), refractive index (RI), fluorescence, electrochemical, evaporative light scattering detector (ELSD). Detectors are chosen based on the residual of interest, the sample matrix, and the sensitivity and selectivity required. Lancaster Laboratories has had success using charged aerosol detectors (CADs) in detecting residuals without chromophores that are not amenable to UV.

**Gas Chromatography (GC)** is another common method of separation and analysis that utilizes flame-ionization detectors (FID) and mass spectrometric detection (MSD). This technique is best suited for volatile and semivolatile organic compounds and is commonly used for residual solvent analysis. Metals analyses can be performed using inductively coupled plasma with optical emission spectroscopy or mass spectrometric detection (ICP-OES, ICP-MS). Polymerase Chain Reaction (PCR) is a technique used to amplify a single or few copies of a DNA fragment by several orders of magnitude. Therefore, it is a great technique for confirming clearance of residual DNA.

**Also, Enzyme-Linked Immunosorbent Assay (ELISA)** is used to detect an antibody or antigen in a sample. There are kits available for host cell proteins specific to a given cell line.

The first step is to determine how to handle the sample. The protein may first need to be precipitated out of solution and then the supernatant can be obtained by centrifugation or filtration. Care must be taken to ensure that the residual impurity is not co-precipitated and/or removed with the protein. The next step may involve further sample preparation, including extraction, distillation and/or cleanup. Extraction approaches may include liquid-liquid extraction with appropriate solvent. Some methods may employ derivatization, which is an approach that modifies the impurity of interest to make it more amenable to a specific detector. Again these steps would need to be evaluated in method development. Next, the determinative approach must be investigated. For example, a volatile organic compound will most likely be best suited for GC, whereas a nonvolatile compound by HPLC. Also, the detector must be chosen based on the analyte of interest, the sample matrix, the sensitivity and the selectivity required. As mentioned, HPLC with Charged Aerosol Detection (CAD) may be a good approach for compounds that do not respond to UV. Also, if the compound can be ionized, MS/MS is usually a good approach due to its selectivity and sensitivity.

Once method conditions are established, the method is evaluated for potential interferences and limit of detection within the particular matrix. Also, the method will be tested to ensure acceptable levels of precision, accuracy, and linearity for the intended application. The method then can be used as a qualified method or a protocol could be drafted to perform a formal method validation.

For more information, call Dr. Kauffman at 717-656-2300, ext. 1377.

# Lancaster Labs offers Melamine testing

by Dr. Tom Lehman, manager, Method Development and Validation

In August 2009 the Food and Drug Administration released a guidance for industry titled, *Pharmaceutical Components at Risk for Melamine Contamination*. The document, identifying various raw materials that are considered high risk for melamine contamination, recommends monitoring of these raw materials for the presence of melamine prior to release into production. The FDA also provided links to methodology for both melamine and cyanuric acid that could be utilized for this testing. Both GC/MS and LC/MS/MS methods developed primarily for food matrix and infant formula are presented.

There are two previous incidents that led the FDA to review the

as a pet food thickener, leading to a mass recall of pet food products. Then in 2008 melamine contaminated infant formula in China was linked to the illness in more than 50,000 infants and to death in at least six infants. It is suspected that melamine was intentionally added to both the pet food products and infant formula to artificially increase nitrogen content in these products. Increased nitrogen content could mislead end users into believing the product had a higher apparent protein content.

Melamine is used in the manufacture of a variety of different

---

**The formation of these crystals has led to renal failure and kidney toxicity, and in some subjects, death.**

---

Cyanuric acid is a structural analogue of melamine and is used in the manufacture of herbicides, dyes, resins and antimicrobial agents; it is also used as a stabilizer and disinfectant in swimming pools. Also, it's

utilized as a component of feed-grade biuret (a ruminant feed additive). Cyanuric acid has a low acute toxicity.

So if both melamine and

cyanuric acid have low levels of toxicity why is there such a concern for melamine adulteration in pharmaceutical products? The combined presence of melamine and cyanuric acid leads to the formation of melamine cyanurate. This compound has low solubility, which can lead to the formation of crystals in the kidneys. Formation of these crystals has been documented in numerous animal studies where the ingestion of both melamine and cyanuric acid was controlled. The formation of these crystals has led to renal failure and kidney toxicity, and in some subjects, death.

Lancaster Laboratories is developing and validating a method to test the majority of the raw materials listed in the guidance document. The method utilizes LC/MS/MS technology, providing greater sensitivity and specificity over other techniques. Lancaster Labs anticipates having this service available to clients in early November. The method that Lancaster Labs provides will meet the guidance document established limit for melamine of 2.5 ppm and will provide quantitative amounts of both melamine and cyanuric acid in various raw material matrices.

If you would like to find out more information on this topic, please call Lancaster Laboratories at 717-656-2300 and ask to speak to a pharmaceutical client service representative.



Dr. Xiaoping Xia, Method Development & Validation principal chemist, develops a method to determine the amount of melamine and cyanuric acid in raw materials, using a Thermo TSQ Vantage LC/MS/MS.

potential impact on melamine in pharmaceutical products. First, in 2007 numerous deaths and illnesses in both cats and dogs led investigators to discover melamine in both wheat gluten and rice protein utilized

products ranging from various resin-based products (countertops, glues, housewares, etc.), cleaning products and industrial cleaners. Melamine has a low acute toxicity and is not readily metabolized.

# Green Team established

by Christina Leslie, manager of Pharmaceutical Drug Release Testing & Clinical Support and John Hook, senior chemist, Metals Department

While Lancaster Laboratories has always been an environmentally conscious organization, we felt it was time to formally implement a team of employees whom would be responsible for driving "green" initiatives.

Among these initiatives, a current Utilities Practical Process Improvement Team has joined the Green Team to increase awareness of the role all employees play when it comes to energy consumption at our laboratory.

Reminders are being posted throughout the facility to encourage employees to turn off lights and computer monitors and to close the sashes of fume hoods when these items are not in use. We are also committed to updating lab equipment to new ENERGY STAR® rated equipment as equipment is taken out of service or when necessary parts are no longer available for repairs. Other initiatives such as replacing light bulbs with more energy efficient light bulbs and switching from CRT to LCD computer monitors are already underway.

All of these actions not only help to reduce our impact on the environment but will also result in significant cost savings for utility expenses.

Also of concern is the usage and disposal of paper. While we want to make sure we're recycling as much of our paper as possible, we can have an even bigger impact by reducing paper usage wherever possible. By not printing or copying emails and documents unnecessarily, or disabling

unused instrument printouts (when applicable), we can cut down paper consumption dramatically.

Another initiative is to improve our recycling efforts. A significant number of hallway recycling containers are being added throughout the facility, and smaller, waste-can sized recycling containers are being offered for use in office areas. By providing



Keeping hood sashes closed while not in use results in significant cost savings in electricity/heating bills as well as reducing the amount of energy wasted when left open.

additional receptacles and putting them in convenient locations, we hope to encourage more employees to recycle. Lancaster Labs also provides battery recycling services, and employees are permitted to bring in used batteries from home for recycling.

So why is this important to our clients? First of all, prices are important to everyone these days. So if Lancaster Labs can reduce the cost of the resources needed to support our business, we can pass along these savings to our clients for our testing services. Secondly, we are seeing that many of our clients factor in whether a company has a sustainability plan and/or supports "green" initiatives when they choose a laboratory to outsource their business. We want to show our current as well as our future clients that we are committed to making environmentally conscious choices throughout our organization. We feel that the establishment of a Green Team to educate our employees, work to improve current practices and support and implement green-friendly programs shows this commitment; not only to clients, but to the environment we all share.

## Lancaster Labs hosts Asahi Planova Training Seminar

As a service to clients involved in the manufacture of biopharmaceuticals, Lancaster Laboratories recently hosted a training seminar on the use of Planova filters for virus removal. Representatives from Asahi Kasei Medical presented a full-day seminar on their virus filtration systems at Lancaster Laboratories. The 22 attendees learned the theory behind size exclusion filtration of viruses and factors to consider in filter selection. The attendees also participated in a hands-on laboratory exercise using the filters. Planova filters have been in use for nearly 20 years and were the first virus removal filters in the industry.

A tour of Lancaster Laboratories' new Biopharmaceutical laboratories was included on the day's agenda. The seminar topic complements Lancaster Laboratories' viral clearance services, which support the viral safety assessment of biopharmaceutical products. Lancaster Labs' role in the process is to evaluate the effectiveness of purification processes, such as filtration with products like Planova filters, by spiking model viruses into the process intermediates. The spiked samples are processed through a scaled-down purification system and then analyzed to demonstrate that the viruses are removed.

For more information on the seminar or viral clearance services, contact Dr. Kate Bergmann, manager, Viral Safety and Viral Clearance, at 717-656-2300.

# Cell Bank Manufacturing Suites and Storage capabilities added

Building on their knowledge of clean room technology, Lancaster Laboratories now offers manufacturing and characterization of a wide variety of mammalian cell banks, including master, working and research banks. To augment this new service, Lancaster Laboratories is tapping into the cold chain management expertise of sister company Fisher BioServices to provide cell bank storage in an on-site, world-class biorepository. Lancaster Laboratories' extensive list of cell banking services provides a single source solution for cell line needs.

Lancaster Laboratories' manufacturing facility is designed to meet current aseptic processing guidelines outlined in FDA's Guidance for Industry: "Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice," and features multiple ISO 7 clean rooms and ISO 5 critical areas. Manufacturing procedures are fully validated and include process simulation studies to ensure the integrity of the manufacturing process. Other available equipment includes class 100 biosafety cabinets, controlled rate freezers, CO<sub>2</sub> incubators and automated cell counting (Vi-Cell®).



Principal Scientist Julie Wilbur performs aseptic filling in Lancaster Laboratories' cell bank manufacturing suite.

"We want to make this process seamless, so that when a client contracts with us for their cell banking needs, they get a comprehensive set of services," explains Mark Kaiser, biopharmaceutical director. He adds that Lancaster Laboratories is well-suited for this work because they already perform the tests required for characterization of cell lines, operate in a cGMP

they manufacture. Their state-of-the-art biorepositories provide efficient retrieval and shipment to clients, including same-day service. A variety of storage options, including vapor-phase liquid nitrogen and liquid-phase liquid nitrogen, are offered to meet client's specific needs. Storage is available in segregated and non-segregated environments. Around-the-clock monitoring of storage areas, along with emergency backup systems and disaster recovery plans, ensure the integrity of samples.

Compliant and efficient transportation of cell banks, using calibrated monitoring probes, eliminates the potential for temperature deviations and related consequences. Cell banks are packed and shipped in full compliance with federal regulations and customer requirements.

For more information on cell banking services, call Pharmaceutical Business Development at 717-656-2300.



This world-class biorepository enables Lancaster Labs to provide on-site cell bank storage through partnership with sister company and cold-chain management expert Fisher BioServices.

Characterization of cell banks is available in the following areas:

- Identity
- Microbial Contamination
- Viral Contamination
- Stability

compliant facility, and have personnel on staff with more than 15 years of cell bank manufacturing experience.

By partnering with Fisher BioServices, Lancaster Laboratories is able to offer secure, compliant storage and shipping options for the cell banks

## Contact us

**For information on services, literature requests, or address changes, please contact:**

Pharmaceutical Business Development  
717-656-2300  
pha@lancasterlabs.com

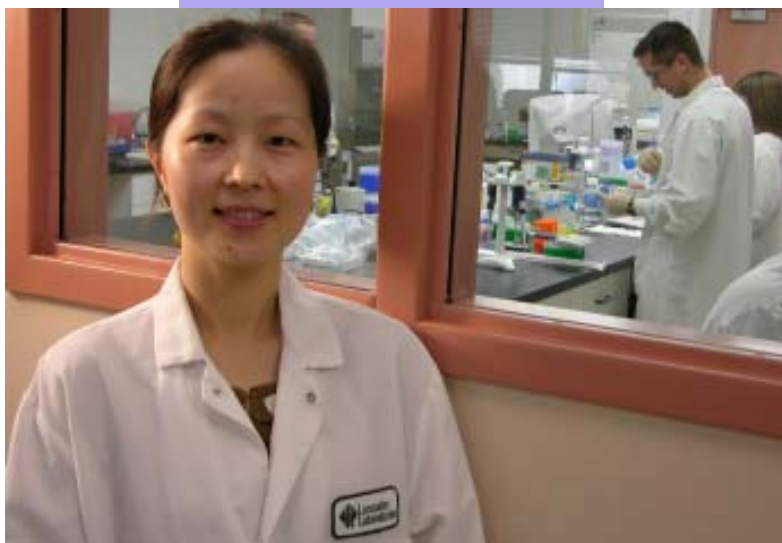
At Lancaster Laboratories, we believe that our people provide our strength. Their dedication to quality, professional competence and hard work is the key element in the company's success. In this regular feature, we introduce you to some of the people who have helped make Lancaster Labs an industry leader.

Dr. Weihong Wang is manager of Lancaster Labs' Molecular and Cell Biology Department. With a bachelor's degree in biology from the University of Science and Technology in China, Weihong came to the U.S. and earned a Ph.D. in molecular and cell biology from Brandeis University. She furthered her education with post doctoral work in molecular medicine/cell and molecular science at Harvard University. She joined Lancaster Labs in early 2009 with nine years of experience in biopharmaceutical drug development and characterization at leading pharmaceutical companies. "It's very encouraging to work in an environment that not only is a GMP facility with good systems in place, but mostly, has people working together to achieve a common goal of serving the client," says Weihong.

### What does your current job entail?

I am responsible for overall management of the Molecular and Cell Biology Services Department to ensure testing turnaround time and all quality metrics are met. More specifically, this includes serving as direct liaison to clients, overseeing in-house assay development/validation projects and client specific projects and maintaining our GMP laboratory. My senior staff and I also try to keep close monitoring of emerging technologies, industry trends and regulatory expectations so we can better serve our clients.

# People are the Chemistry



Molecular and cell biology manager  
Dr. Weihong Wang

### What is the scope of your group?

We are a team of 10 people, including three Ph.D. level scientists. All our analysts are trained in multiple assays in the Molecular and Cell Biology area. With our experienced scientists, we can provide different services to our clients, depending on their specific needs. For example, for a small or virtual company that does not have in-house assay development capabilities, we can develop from scratch a potency or residual assay that is suitable for release testing or stability studies. For other clients who have an R&D method but lack experience in method validation, we can optimize the methods prior to validation to ensure assay performance. We will work closely with our clients to develop a program that best suits their

needs and helps shorten the development time of their drug candidates.

### How would you characterize your leadership style?

I'd like to be able to bring the best out of everyone in the team. I think it is important to recognize that people have different personalities and working styles and take advantage of that instead of trying to mold everyone into the same shape. Also, I believe honest feedback is critical. Management needs to let people on the team know where they do well and where they need to improve so they understand the expectations and feel in control.

### What awards/special corporate recognitions have you or your group received?

Our department received the Labs' Triple Crown Award for four consecutive months (June-September) for meeting our department revenue goal and quality and TAT metrics. We were challenged with high-volume testing on top of multiple in-house assay development projects. Everyone in the department worked together and put in many weekend hours to get the testing done on time. I am so fortunate to be part of a great team that is energetic, goal orientated and self motivating!

### How does your group's work impact/benefit society?

Our team performs the release testing of biopharmaceutical drugs, and our work ensures that drugs that are released to the public are effective and are free of contaminants that may cause detrimental effects if administered to patients. This is a great responsibility.

Lancaster Laboratories  
2425 New Holland Pike  
PO Box 12425  
Lancaster, PA 17605-2425

RETURN SERVICE REQUESTED

Presorted  
Standard

U.S. Postage  
**PAID**

Lancaster, PA  
Permit No. 87

## Visit us at...

### **AAPS Annual Meeting:**

November 8-12, Los Angeles, CA

### **Well Characterized Biologicals:**

November 10-12, Bethesda, MD

**WCBP:** January 24-26, Washington, DC

**InterPhex Puerto Rico:** March 4-5, San Juan, PR

**PDA Annual Meeting:** March 15-19, Orlando, FL

**InterPhex:** April 20-22, New York, NY

## Newsmakers

**Eric Lingenfelter**, group leader; **Henry Evans**, chemist; and **Wesley Atkins**, senior chemist, Method Development and Validation Department, and **Harolyn Clow**, microbiology manager, authored Part 1 of the cover article, "How to Improve Cleaning Processes," in *Pharmaceutical Formulation & Quality*, June 2009.

**Eric Lingenfelter**, group leader; **Henry Evans**, chemist; and **Wesley Atkins**, senior chemist, Method Development and Validation Department, published Part 2 to the aforementioned article titled, "Contamination Control, Cleaning Validation Procedures," in *Pharmaceutical Formulation & Quality*, July/August 2009.

**Travis Emig**, director, and **Nathan Wisniewski**, manager, both of Pharmaceutical Chemistry, wrote, "Rapid Growth of Full Time Equivalent Staffing Programs" whitepaper in *Contract Pharma, Pharmaceutical Technology* and *Biopharm International*.

**Dr. Timothy Oostdyk**, executive vice president and COO, was featured in "Industry Leaders Q&A" in *Pharmaceutical Technology*, September 2009.

**Dr. Jon S. Kauffman**, director of Biopharmaceutical Services and Analytical Method Development & Validation, provided "Contract Consulting & Pharmaceutical Services" editorial comments for *Biopharm International*, September 2009.

**Dr. Jon S. Kauffman**, director of Biopharmaceutical Services and Analytical Method Development & Validation, wrote, "Analytical Strategies for Monitoring Residual Impurities Encountered In Bioprocessing," whitepaper in *Biopharm International* and *Pharmaceutical Technology*.

**Eric Hoffman**, director of business development and strategic marketing, provided editorial comments in "Having Your Say" for *Contract Pharma's* 10th Anniversary special, October 2009.

**Dr. Vikas Dhingra**, group leader of biochemistry, will present two technical posters, "Characterization of a Therapeutic Glycoprotein using SDS Capillary Electrophoresis (CE-SDS)" and "Optimization Strategies to Determine Charged Protein Variants in a Therapeutic Protein Using Capillary Isoelectric Focusing," at AAPS 2009.

**\*Please visit [lancasterlabs.com](http://lancasterlabs.com) to view the aforementioned presentations and articles.**

*Pharmaceutical NEWS*  
is published for  
clients, employees, and associates  
of Lancaster Laboratories Inc.  
Editor: Lisa Bamford  
(717) 656-2300, Fax: (717) 656-2681  
web site: [www.lancasterlabs.com](http://www.lancasterlabs.com)