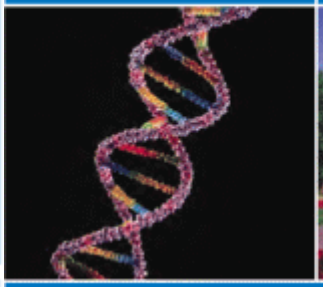
ISPE Boston Area Chapter
ENGINEERING PHARMACEUTICAL INNOVATION

www.ispe.org/boston




NEWSLETTER

February 2008, Volume XVIII, No. 1

Previous Issues

October 2007, Volume... (10)
December 2007, Volume... (13)

Newsletter Archive

Return to the Table of Contents | Printing Instructions

Save page as PDF

President's Message: When Cancer Hits Home

Hello ISPE Boston Area Chapter Members,

My mother's been diagnosed with cancer. It happened this past summer. The oncologist at the Lahey Clinic in Burlington told her the exhaustion and discomfort she was feeling was due to non-Hodgkins lymphoma (NHL) - a cancer that causes certain types of white blood cells to grow uncontrollably with the potential for planting malignant tumors throughout her body.

In shock, I rushed her over to Dana Farber in Boston where her diagnosis was confirmed and she was immediately scheduled for several months of lengthy infusions. My wife and I began taking turns driving her from Southern New Hampshire to Boston for each 8 hour stint of the slow infusion of the drugs that we prayed would cure her.

Reading the label on the bottle of one of these drugs that hung above her bed and slowly dripped into her veins, I noticed a vaguely familiar word, "Rituxan." It didn't click with me right away but after a while I realized that this was a drug that my company in a small way helped make. It was several years earlier that we participated as part of the team of engineering firms, vendors, and support personnel (including many ISPE Members) helping to produce this particular drug. What an incredible coincidence. Now I was praying it would save my mother's life. What are the chances of something like this happening?

Well, as I learned through the internet that night, with over 58,000 Americans diagnosed with NHL annually and over 360,000 Americans currently living with the disease, the chances are pretty good. In fact, Rituxan (also known as Rituximab), a monoclonal antibody developed using recombinant DNA, approved by the FDA in November of 1997 and co-marketed by Biogen Idec and Genentech, has become the first line of defense against NHL. In total, over 960,000 Americans have been treated with Rituxan to date.

Rituxan works by attaching a biological "flag" onto specific proteins on the surface of lymphoma cells, causing the body's own immune system to target and destroy only these particular, out-of-control cells. The side effects are much less toxic than the drugs used before Rituxan's arrival. For example, my mother's hair didn't fall out.

This experience got me to thinking about all the other projects and therapeutic life saving drugs my company and other ISPE Members have worked on over the past 20 years. Do we ever stop and think about the truly astonishing, almost magical, life saving or life enhancing power of the products we are helping to manufacture or bring to market? Do we really understand the hope and value these therapeutics bring to families like mine?

My family and I are very pleased to report that my mother's cancer is in remission. It will never disappear, but thanks to Rituxan, it has been entirely brought under control - like 43 percent of similarly treated patients, according to one early study. Thank you, Biogen Idec and Genentech for saving my mother. And thank you to all the ISPE Members (many of you I'm sure don't even know you were involved) who assisted in any way in bringing this drug and others like it to market.

This traumatic incident makes me proud to be part of this industry and prouder still to be an ISPE Member. ISPE, founded and run by volunteers with a real interest in promoting pharmaceutical innovation, continues to promote knowledge, career and networking opportunities right here in Boston. It is also noteworthy that the Boston Area Chapter received impressive recognition during the recent ISPE Annual Meeting in Las Vegas by winning the award for "Innovation in Events," the only such award amongst all Chapters in North and South America.

As a Boston Area Chapter member, you might have joined approximately 100 festive members for the very successful New Year Social Event held at Flat Top Johnny's in Cambridge this past January 10th. Students from the Northeastern, Tufts, and WPI Student Chapters also attended. You might have enjoyed the January 15th presentation at the Royal Sonesta on the current world wide standards for submitting new drug applications. This fascinating event involved three very knowledgeable speakers: Michelle Herrara Foster, Ph.D. and Fiona Sibley, both of CTD Quality Consulting, and Yolanda Hall, MSDRA, of Datafarm.

As a Boston, ISPE member, you might also be planning to attend the February 13th Biotech Forum with MIT at the Sonesta, the March 11th tour of Millipore in Bedford, the March 18th regulatory discussion at Biogen Idec or the April 16th S88 presentation at the Sonesta. If you're involved in any way with developing, commercializing, manufacturing or promoting life saving and life enhancing drugs and medical devices, you're sure to get something of value from ISPE.

And thanks again, from the family of a patient whose life depends on it, for your valuable efforts in moving this industry forward.

Sincerely,

Rick Pierro, President, ISPE Boston Area Chapter

Upcoming Chapter Events - Mark Your Calendar

February 13, 2008
Register Today at http://www.ispe.org/page.ww?section=Boston+Area+Chapter&name=Events
Joint Meeting with MIT
Continuous Improvement in Biologicals Manufacturing: An Opportunity for Process Analytical Technology

Speaker:

Professor Charles L. Cooney
Department of Chemical Engineering
Massachusetts Institute of Technology

Royal Sonesta, Cambridge, MA

March 11, 2008 - Plant Tour
Millipore
Bedford, MA

March 18, 2008 - Regulatory Seminar
Biogen Idec
Cambridge, MA

May 20, 2008 - Water Seminar
Royal Sonesta
Cambridge, MA

June 17, 2008 - Facilities Seminar
Royal Sonesta
Cambridge, MA

August 18, 2008 - Annual Golf Outing
Ferncroft Country Club
Middleton, MA

Project Management: "The Tail Wags the Dog?

by David MacDonald with photos by Peter Teague

Project Management came to the Boston Area Chapter of ISPE on Tuesday, November 13, 2007. The room was full at the Royal Sonesta in Cambridge, as two excellent speakers explored several facets of the complex area of project management. One speaker focused on small projects and the creation, care and feeding of project teams and the second speaker focused on how to control massive capital projects and how to develop a global project management standard for a multinational.

Niall Johnson, Associate Director of Capital Projects/Facilities, Engineering & Planning for Millennium Pharmaceuticals, spoke first. He described several drivers for utilizing project management and project management tools. First, the FDA has estimated that there is $60 billion of opportunity cost in the pharmaceutical industry. In the FDA's quest to lower drug prices, the industry will be forced to start minimizing that opportunity cost. Project management is just a set of tools to allow us to do business better. In addition, there is a need to leverage individual project success to business success, which is, after all, our overall goal. Project management includes tools to make sure that individual project goals are aligned with the overall company business goals.

Attendees enjoyed a light buffet dinner and networking reception before the preseentations.

Niall Johnson of Millenium Pharmaceuticals mixed factual information and amusing anecdotes for a presentation that was both enjoyable and informative.

Johnson defined a project as a set of activities having both a start and a finish, leaving a wide range of topics as possible projects. Only about 50 percent of a typical project is in the execution of the project. The rest is in the initiation, planning, verification and closure. The project can succeed or fail just as easily in these phases as in the more visible execution phase. The challenges faced in a project are different for each level of stakeholders - the industry, the individual business, the specific project team and the individual project team member.

One of the keys to project success involves addressing Project Risk. Putting your head in the sand about the risks in a project is not a good option. Likewise, saying that we want "no risk" is unacceptable. Instead, we need to not rely on intuition, but identify what the real risks are and manage, monitor, and mitigate those items. But the list of risks that you are managing needs to be short (less than 10) and well-prioritized (those risks that are real and important).

Johnson discussed two key project documents, the Project Initiation Document and the Project Planning Document. The Project Initiation Document is the project charter. It should be short, 3-4 pages, and should clearly state the business case, project boundaries, risks, constraints, expectations and success criteria. The Project Planning Document has more detail, delving into user requirements, process block flows, project work breakdown structure and preliminary schedules (less than 15 tasks). This document should also clearly define the success and acceptance criteria.

Wrapping up his section, Johnson reminded the attendees that all projects are change and so are challenging. The real definition of project success is "Would you be willing to do the project again with the same people?" The soft side of project management and project leadership are as important to the success of the project as the technical skills.

Jeremy Gross, a Principal from PMA
Consultants, then continued the evening with a

session on Project Controls, Schedule Integration and Project Reporting. Gross reminded the audience that in the structural construction side of the business, GMP means guaranteed maximum price, having nothing to do with the FDA (so we have to keep a close eye on our three letter acronyms).

He went on to discuss Project Controls. This is not project accounting, but a tool kit for project management, used to ensure that past mistakes are not repeated. It includes a disciplined approach to estimating, scheduling, cost controls, monitoring, trending, forecasting and reporting the project. And it includes a feedback loop to capture data and lessons learned. Gross reported that the benefits of using this tool kit include early warning signs and reliable forecasting as well as lower cost growth, lower total cost and less slippage in the project schedule.

Jeremy Gross of PMA Consultants offered many valuable insights based on his extensive project management experience.

PMA was involved with developing a global standard for project schedule integration for large scale projects for Johnson & Johnson. One single large project could consist of 30,000 items, so no single person looks at all the items. Each smaller portion of the project has to be managed with a schedule and plan which an individual could understand. These individual plans then have to be wrapped up into the overall master schedule. Only with a very disciplined approach could all of the sub-project schedules be managed, integrated, updated and reported successfully. The updating of the project progress and its schedule becomes an intricate task in itself, with progress data reporting cut-off dates and schedule-update dates.

Even the reporting of the status of a project becomes a disciplined art. Gross pointed out that there needs to be multiple levels of reports generated, depending on the needs of the report users. At the highest level, there are Executive Level Reports which quickly capture the essential high-level information on project costs and schedule. They must be quickly and easily read and understood, and should be in a standardized format. Dashboards have proved useful at this level to quickly convey the necessary information. Just taking a report from Primavera will not work at the executive level. Meanwhile the Project Manager needs to be looking at detailed tabular reports and resource availability and demand curves. These need to be both customized for the needs of the project manager and as standardized as possible for consistency and ease of understanding.

PMA was so successful in helping J&J on one of their massive capital projects that J&J senior management asked for their help in standardizing the company's global approach to capital project management. This demonstrated the versatility of the project management tools that both speakers had described, covering the range between a conference room renovation to a global multi-billion dollar a year capital program.

For more detail, readers are invited to view the presentation overheads on the Boston Area Chapter Website at http://www.ispe.org/page.ww?section=Boston+Area+Chapter&name=Events

Another Successful Holiday Party at Flat Top Johnny's

by Gene Dennen

If you're an aspiring pool shark, you should have joined us at Flat Top Johnny's on the evening of January 10th. The occasion was the Chapter's "holiday party," rescheduled and renamed after our Christmas Party had to be cancelled

due to the snowstorm on December 13th. There were better than 10 pool tables made available to us and, as far as I could observe, there was no one present who wasted their youth at some pool hall or paid their way through graduate school by hustling the student body with their pool cue.

What I'm saying is, if there were any hustlers present, they surely weren't playing pool. The only hustling I did see going on was begging for blue raffle tickets. These were very valuable commodities good for a free drink at the bar. Since no one should drink on an empty stomach, a very nice buffet was offered, with a variety of hot appetizers: teriyaki sticks, bacon-wrapped scallops, stuffed mushrooms and buffalo wings, to name only about half the selections available. I don't know why it is, but for some reason food always tastes better to me when I'm consuming it standing up. The featured brew was a wheat beer called UFO and, although I don't usually like wheat beers because of their yeasty aftertaste, I'm glad I gave this one a try - it was delicious!

Because the holiday season is so hectic with all the additional obligations that get stuffed into a two or three week period, several people commented to me that we consider doing our holiday social in January every year. I certainly can understand their point but I missed the toy drive and the US Marines normally in attendance when our social takes place before Christmas.

Speaking of gifts, let me not forget to mention the sponsors that donated the great items that were given away as door prizes. And I'm talking about Celtics tickets and $125 gift certificates to swank downtown restaurants. To A/Z Corp, Columbia Construction, Integra Companies, INTERPHEX 2008 and Flat Top Johnny's - a big thank you. And, as always, our thanks to the hardworking volunteers on the Chapter's Social Events Committee who worked doubly hard this year to stage a successful event in spite of the uncooperative New England weather. See you next year!

Its All in the DOCS: Planning CTD/eCTD CMC Submissions

text and photos by Deepen "DJ" Joshi

At the January 15th Educational Program (EP), the ISPE Boston Area Chapter continued its mission of combining timely information on a topic of current interest to the industry with an opportunity for informal discussion and networking among peers. The topic of discussion that evening - Common Technical Document (CTD), the current worldwide standard for content and format of submissions of Investigational New Drug Applications (INDs) and New Drug Applications (NDAs) - was a welcome one and the first time the Chapter has devoted an EP to the topic of regulatory documentation.

The program was held at the Royal Sonesta in Cambridge, a convenient location that offers multiple parking options nearby. As usual, opportunities to socialize and mingle with various industry professionals were made available along with complimentary food, beverages and desserts. Also as usual, the evening provided a great mix of education, experience, networking and entertainment.

Participants engaged in conversations at the carving station before the presentations.

Rick Pierro, President of the Boston Area Chapter, jump-started the program by sharing some of the Chapter's upcoming events and giving a warm welcome to the panel of speakers, all of them distinguished experts from the regulatory domain. Speakers included Michelle Herrera Foster, PhD (CTD Quality Consulting), Fiona Sibley (CTD Quality Consulting) and Yolanda Hall (Datafarm), all of whom gave formal presentations; and panelists James Blackwell (BioProcess Technology Consultants) and Tish Webber (Wyeth BioPharm).

Dr. Herrara Foster, CTD Quality Consulti

prepare CTD. She started by describing the background and expertise of each member on the panel to demonstrate t diversity the panel offered and encouraged the audience to engage in a two-way dialogue with the panelists following explained the many acronyms, considered standard terminology in the industry, to be used throughout the presentatio

She then went on to describe the data which, under the current EU regulations, has to be contained in Module 3 so th drug/biologic in question is of appropriate pharmaceutical quality. She also discussed the importance the electronic ve Document (eCTD) may have now and in the future. The eCTD is expected to fully replace the "paper" CTD, thereby re received by regulatory authorities on a daily basis to a reasonable level. In addition she stated that the CTD is require marketing applications, "highly recommended" by FDA for NDA/BLA and required by Center for Drug Evaluation and R submissions.

During the course of her presentation, Dr. Herrara Foster suggested treating CTD as a live document throughout the s the advantages and challenges of that approach. She also skimmed through the following sub-topics: key CTD needs efficiency to the process, difference between various sections of Drug Substance (DS) and Drug Product (DP) for Mod Module 3 to the NDA, BLA and MAA. She identified the new sections required by the CTD and listed high level points of CTD from IND (Phase 1). She enlightened the crowd with examples of Module 3 reports and types of reports, name level summaries (for Module 2) and reports on file for inspection. The panelists contributed additional information as n a different viewpoint or example to clarify the issue at hand. This exchange allowed the audience to appreciate the reg and what is considered an appropriate and balanced approach.

The second part of the EP was dedicated to the presentation of CMC CTD case studies by Fiona Sibley. The case stu development, viral clearance and sterilization validation helped the audience to understand the applicability of CTD to they may not have received a comprehensive understanding of the mundane challenges in the preparation of CTD, th through which the attendees could view and better appreciate the intricacies involved in CTD/eCTD development. In h recommended that submission-ready validation reports and other reports be written in advance so that summaries an CTD at filing time, thereby saving effort and reducing stress. The participants acknowledged that following these recor in increasing the efficiency of the process.

Following the CTD overview and case studies presentations, Yolanda Hall covered Electronic Common Technical Doc She said that the eCTD is a part of the ICH initiative to provide a common format for the industry-to-agency transfer of acceptable across the ICH regions of the United States, Japan, and the European Union. She also explained how the "XML backbone" as a new way of approaching electronic submissions. This benefits both sponsors' organizations and mechanism to record all interactions and highlighting changes between submissions.

She suggested that organizations that have a defined CTD process should strongly consider evaluating multiple paths for the transition to eCTD, allowing them to select the best path for a seamless transition. She added that organizations find it difficult to define the right moment to become eCTD compatible due to the "deal breaker" attitude of "once eCTD, always eCTD." She indicated that eCTD is targeted for acceptance in the EU by 2009 and that companies need flexible systems that would enable them to move toward full eCTD submissions using a

staggered approach. She also commented that medium- and small-sized companies may have shorter learning curves than large companies.

Ms. Hall provided highlights on eCTD specifications Module 3, reiterating that granularity is the key to successful eCTD. She explained the relationship between XML and Templates as it applies in Modules 2 and 3, and the importance of defining the directory structure, file organization, file names and their boundary values. Participants requested further clarification on the technological investment (small scale investment vs. large scale investment), Life Cycle Management (LCM) of submissions as well as of documents, including correlation between the two. She remarked that benefits include the efficiencies gained by content reuse between submissions, the ability to submit simultaneously to the three largest pharmaceutical markets around the globe, and the simplification of the maintenance process throughout the submission lifecycle enabled by the XML backbone structure.

Yolanda Hall, Datafarm, discussing eCTD fundamentals.

During the final wrap-up discussion, the panelists sought to summarize some of the key themes of the three presentations. They handled the follow-up questions round-robin style, providing a variety of perspectives, solutions and applicability, where possible, to add further clarification. Audience members working in the same domain also joined in, sharing strategies that are being used in their own companies.

In sum, attendees gained a better understanding of CTD and eCTD and their applicability to manufacturing, process automation and related domains, and were able to make new friends and meet with existing ones while spending an evening on the cutting edge of all that is new and exciting in the industry. This certainly is priceless!

The Challenges in Integrating a Process Control System with Skid-based Equipment: A Case Study

by Robert Patrick

Most projects involve the same questions and challenges regarding the integration of the Process Control System (PCS) with skid-based equipment. This case study examines two approaches to Process Control Systems integration. In the first, the skid vendors were responsible for all aspects of the design, development, documentation, and factory testing of the control system with the system integrator handling only integration of the skid after delivery on-site. With the second approach, the system integrator was involved from the outset, taking the lead role in the design and development of the operator interface, data collection, and reporting while providing guidance to develop the control software.

This case study was a facility expansion, executed in two phases over a period of three years at a cost of $120 million. The project included equipment typical to biotech facilities such as utility skids for Pure Water (PW), Water for Injection (WFI), and Clean Steam, as well as process equipment such as buffer preparation tanks, bioreactors, clean-in-place (CIP) skids and lyophilizers. Phase A consisted mainly of the addition of utilities in one of the new areas of the facility, while Phase B included additional utilities and the process equipment. Both approaches need to consider the following items during the planning phase of a project:

- What are the PCS requirements?
- What equipment should be integrated with the PCS?
- What are the responsibilities of the skid vendor versus the PCS systems integrator?
- What hardware and software are acceptable (including revision information if possible)?

These questions should be addressed clearly in the User Requirements Specification (URS) for the PCS. The PCS URS should be provided to the skid vendors during the bidding process and agreed upon as part of the PO. The PCS requirements for this project included:

- Uptime (redundancy)
- Local control with view-anywhere capabilities
- Data collection of Process Measurements, Alarms and Operator Events to a central database
- Remote Notification of Alarms
- Reporting (Batch, CIP, SIP) ad hoc
- Consistent displays for ease of operator use
- 21CFR Part 11 compliance as defined by the customer

The equipment in the facility was categorized into three different types based on the amount of required integration with the PCS.

With the Type A Equipment, the PCS was used to monitor and control all functions of the equipment. The PLC code was provided by the equipment manufacturer, while the PCS systems integrator provided the SCADA. Type A equipment included the PW, WFI, Clean Steam, CIP, and Bioreactor skids.

In the Type B Equipment, the PCS system provided no control or monitoring except for remote alarm notification. Type B equipment included operations such as the Glassware Washer, Autoclave, Depyrogenation Oven, and Lyophilizer.

For Type C Equipment, the equipment vendor did not provide any controls. The PCS system was used to monitor and control all parameters for the equipment with the PCS systems integrator developing all control specifications for these items. Type C equipment included utility storage and distribution systems, buffer preparation tanks, and solution preparation tanks.

During Phase A of this project, the skid vendors were responsible for the PLC programming, screen generation, documentation (SDS, FAT, SAT), and testing. The PCS systems integrator was then responsible for the integration of the skid after delivery on-site. In reviewing Phase A, the following issues were identified with this approach:

- Inconsistencies of core modules, such as manual control of valves and pumps, led to differences in the operator interfaces. These inconsistencies caused operator confusion and increased training difficulties.
- Skid vendors were forced to use unfamiliar SCADA software that increased the time required for development, and in some cases, required customer assistance to configure the software.
- There were increased risks because some skid vendors were unfamiliar with best practices for development, making tag, screen, data collection and security conventions more difficult to implement.
- Modifications that were required to achieve integration once the skid arrived on-site became an additional cost instead of being included in the initial development of the equipment's control system.
- Some skid systems included their own data collection, database, and reports. For these systems, integration with the PCS was difficult and provided little customer benefit.
- Inconsistency of document formats between vendors made the review process, test execution, and validation more difficult for the customer. The customer and validation contractor used the developed design and test documents to create validation documentation.

In an effort to improve the process, Phase B used a different approach. The skid vendors were responsible for the control programming, provided input for SDS documentation development and assisted during the FAT execution. The PCS systems integrator provided core PLC logic modules to the skid vendors and was also responsible for

screen development, data collection, reports, documentation (SDS, FAT, SAT), and test execution. The advantages to this approach included:

- Controls - By providing sample code for the skid vendors, the PCS systems integrator was able to use standard templates for core items such as auto/manual control of valves and pumps.
- Design and development - The PCS systems integrator served as a second set of eyes with industry-wide experience to help design and develop the skids.
- Screens - The PCS systems integrator was involved in the development of standard formats. These formats, which included screen layout, tag and screen naming conventions, security, and navigation, enhanced the effort to bring consistency throughout the facility.
- Documentation - Consistent document formats were familiar and led to increased efficiency for customer review and testing.
- Testing - The PCS systems integrator was involved during the FAT and therefore was able to identify issues or problems before the skid was shipped to the customer site. Improved integration and testing during SAT and commissioning also occurred because the PCS systems integrator was very familiar with the equipment and documentation before delivery on-site.
- 21CFR Part 11 Compliance - With the systems integrator responsible for central data collection, security, and audit trails, a more uniform system was developed to meet customer requirements.
- The systems integrator was also able to provide a second, local source of customer support for the skid controls.

From continuous involvement on both phases of the project, the system integrator provided core PLC modules, standard screen development, document templates and test execution that met the customer's needs for consistent displays, central data collection, and site-wide security. The following lessons were learned and recommendations emerged:

- Specify upfront in the PCS URS the specific responsibilities for the PCS systems integrator and skid vendors so discrete roles remain defined to avoid overlap of responsibilities and cost overruns.
- Involve the PCS systems integrator in the development of the skid software from the start of the project. It helps if this involvement includes having the PCS systems integrator present during the FAT.
- Where applicable, specify standards for the skid vendors to follow so each vendor meets the same criteria and serves the customer's needs for a user-friendly, seamlessly integrated system.
- Coordinate software development at the same level as the mechanical and electrical portions of the skid. Such coordination makes the integration process smoother and results in a more functional system when the project is complete.
- Use the expertise of the PCS system integrator, who usually has a view of the bigger picture or the total facility and sustains a long-term relationship with the customer, to provide help with future needs and longer range planning.

Robert Patrick has been with Superior Controls in Seabrook, New Hampshire for over nine years, where he is employed as a Project Manager. He holds both a BS and MS in mechanical engineering and has 13 years of experience in the automation and controls industry, with an emphasis in biotechnology over the last seven years.

Optimizing Your Steaming Operation: A Steam-In-Place Primer

by Pietro Perrone

Steaming is an important operation in a facility that handles biological products. When applied properly it provides reassurance for microbiological control and safety. The main function of steam in a process is to expose the equipment to a sufficiently high temperature for a specified time to achieve destruction or reduction of the unwelcome organisms. Selecting an appropriate steaming arrangement is important as it can have a significant effect on the cost and operation of the plant since a typical production facility can include many steam points. This article identifies the

main Steam-In-Place (SIP) components and the various ways they can be arranged at the steam/condensate collection points. The article also provides guidance on how component selection can shift costs between capital and operating budgets while helping to determine if an automated steaming operation can provide a satisfactory return on your investment.

Steaming operations

Fundamental Steam-In-Place (SIP) processes consist of three main steps/activities:

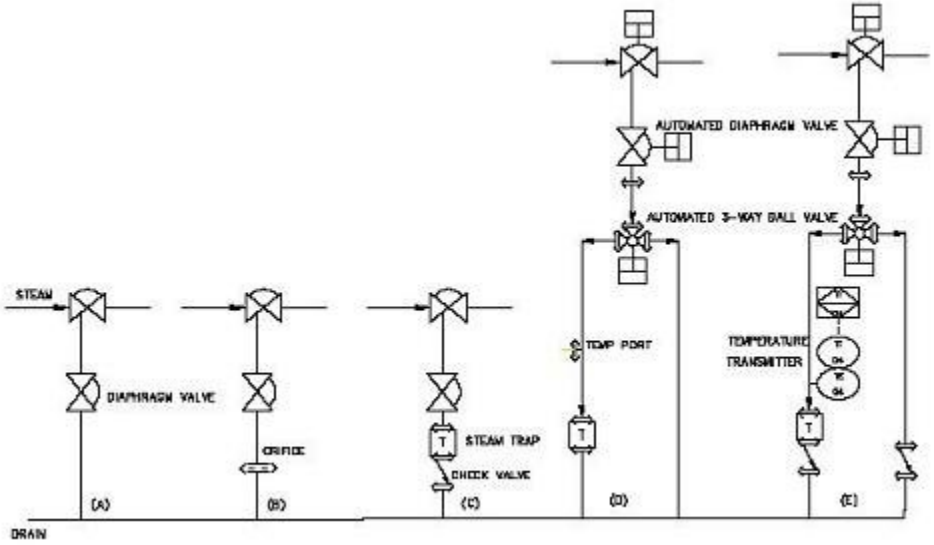
1) Apply steam.
2) Remove condensate.
3) Monitor temperature and time.

Engineers have developed a variety of innovative ways to implement these steps into the specific constraints of a process. The different ways are often a balance between the components used at the steam points and the amount of labor needed to monitor and validate the effectiveness of the steaming operation. A satisfactory steaming operation is one that yields an acceptable level of confidence in the steaming operation and one that:

- confirms that a microbiologically effective temperature and exposure time is achieved, and
- removes steam condensate effectively.

There is an array of components that can be applied to achieve an effective SIP operation. Several representative SIP arrangements are presented in Figure 1. Although each arrangement varies in the level of complexity, they all can provide effective steaming.

Figure 1. Typical steaming arrangements at steam/condensate collection points. Three are for manual operation and two for automatic operation. Alternate permutations of these are possible with equivalent SIP capability.



Description of the various steaming components and SIP arrangements

Manual diaphragm valve (Fig. 1A) - manual operation.
This arrangement is the simplest method to steam. The primary function of the diaphragm valve is to isolates process lines from the steam manifold which typically is also the pipe specification breakpoint. This valve can be used for steaming if the valve is opened slightly to allow passage of steam or condensate. This option is the least expensive from a component perspective. It is, however, costly in terms of steam loss and it can be environmentally unfriendly. Additionally, this simple arrangement requires the most attention to record and validate that sufficient steaming is occurring. The combination of labor cost and the wasted steam cost make this an operationally expensive option.

Orifice plate (Fig. 1B) - manual operation.
Using an orifice plate that allows steam to escape continuously provides for another simple operation. It is easy to implement and is relatively reliable since there are no moving parts. The orifice provides more consistency than just opening a diaphragm valve. Similar to the diaphragm valve arrangement (Fig. 1A), the cost for components is low. The amount of labor to monitor and validate operations is significant. Correspondingly, the labor cost and wasted steam cost make this process operationally expensive.

Ball valve with orifice (not shown)
Replacing the orifice plate with a ball valve that has a small orifice provides for an improvement in operation. This setup is relatively simple as well. It has the same cost advantages and disadvantages as the orifice plate. Since a valve is replacing the orifice plate, it can be used for flushing the process pipe at process flow rates. The valve "closed" position allows the steam to pass through the orifice. The other, "open" position of the ball valve is for the full flow of flush liquid. This allows for flushing of the diaphragm valves and the corresponding process and steam lines.

The steam trap - an effective component for energy utilization.
Steam traps are typically applied in steaming operations. They are effective in extracting the most energy from steam. Although the complexity of the operation increases when a stream trap is added to the operation, the additional material cost is offset by the energy savings that result from minimizing steam loss. Steaming operations need to be analyzed from an engineering perspective to optimize heat transfer. Piping arrangement and effective removal of air from the piping is important for effective heat transfer. A detailed tutorial[(1)] on the thermodynamics can be found at the Spirax Sarco website (www.spiraxsarco.com/learn). The steam trap is a critical component in the process. Its function is to maintain a closed system for the steam while allowing condensate to exit.

Three types of steam traps are available. They are classified by the method each uses to separate steam from condensate as described in Table 1. You can find a detailed description on the features of each unit in Millipore's Technical bulletin, Lit. No. TB011EN00 [(2)]. The thermostatic type is the one most appropriate in biotech/biopharmaceutical applications. The steam trap maximizes energy utilization but increases the complexity of the operation. This complexity includes additional piping that needs to be cleaned. Since the steam condensate flow is relatively low, the standard steam trap hinders a full flow flush of the process line that is often needed for Cleaning-In-Place (CIP) protocols. Both of these issues are addressed in the steaming arrangements and components shown in Fig. 1C-E and described in the upcoming sections.

Table 1 - The types of steam traps

	Mechanical	Thermodynamic	Thermostatic
Method of Operation	Detects density difference between steam and condensate	Detects velocity difference between steam and condensate	Detects temperature difference between steam and condensate

Steam trap with check valve (Fig. 1C) - manual operation.

This is one of the simplest arrangements for the use of a steam trap. The diaphragm valve upstream of the trap segregates the process piping from the steam piping. This valve is manually opened during SIP and the steam trap will do the rest in separating steam from condensate. The check valve downstream of the steam trap prevents backflow. The steam piping is typically very small (½-¾ inch) which creates a section of low flow in the process piping. High flow steam traps have been applied to allow full CIP/flush flows. Since this arrangement is based on a manual operation, the operator monitors/records the temperature and confirms the temperature is maintained for the pre-defined time. The cost of the additional components in this arrangement is offset by the energy savings realized by maximizing the use of the steam. The manual operation still results in a significant labor cost.

Steam trap with parallel flush line (Fig. 1D) - automatic operation.
Automated operations provide a significant benefit in SIP processes. This arrangement will automatically activate steaming for a predetermined time. The 3-way ball valve allows for flushing to drain during the CIP process. The operator can use the sample port to insert a temperature probe and confirm appropriate temperature is reached. This temperature mapping procedure is typically done at all steaming points during validation. It can be done periodically during normal operations to confirm consistency in performance. This layout balances and minimizes component and labor costs.

Steam trap with parallel flush line and check valves (not shown) - automatic operation.
This arrangement is similar to Fig. 1D with the addition of check valves in each drain line. These are not typically critical in the operation, but have been seen in numerous processes where automatic operations are applied. It primarily provides a higher level of safety with minimal additional cost.

Steam trap with flush line and temperature monitoring (Fig. 1E) - automatic operation.
This full automatic operation proves its value in the labor savings that are realized while providing full monitoring and documentation of operation. There is a higher cost at the outset for the components and for the software. This arrangement yields the least risk in the operation as temperature and time are recordable and all CIP/flush sequences are automatic. This layout minimizes labor costs and minimizes risk for improper CIP/SIP as all process sequences are automatically controlled.

Table 2 summarizes the operational features for the five arrangements and provides guidance on the expected costs for components and labor. The more automated options (D-E) carry a relatively higher cost for the components while minimizing the amount of labor. These options are also more repeatable and reliable due to the automatic execution of operating sequences and the automatic recording of operating data.

Table 2. Material and labor cost for steaming operations

Arrangement →	**A**	**B**	**C**	**D**	**E**
Time tracking	Operator	Operator	Operator	Electronic	Electronic
Temperature	Temp sticks	Temp sticks	Temp sticks	Thermometer	Transmitter
Steam flow/loss	Yes	Yes	Minimal	Minimal	Minimal
Condensate flow	Minimal	Minimal	Yes	Yes	Yes
Estimated relative	1X	1.2X	2X	5X	7X

component cost					
Expected labor cost	High	High	High	Medium	Minimal

SIP operations can vary widely. The components and methods highlighted in this article cover a range of these operations. The automated and instrumented SIP arrangements typically result in a higher initial cost but provide for reduced long-term labor cost. The manual arrangements minimize initial costs, but result in higher operating/labor costs and potentially a higher risk for improper operating conditions. The optimized steaming operation is often a unique balance between the cost of the components and the labor required for the operation. Steaming arrangement can be developed to meet specific budget constraints while maintaining SIP effectiveness.

---

1. Steam Engineering Principles and Heat Transfer, Spirax Sarco website. www.spiraxsarco.com/learn.
2. Principles of Steam-In-Place, Millipore Technical bulletin, Lit. No. TB011EN00 Rev. B, May 2003. http://www.millipore.com/.
3. Designing a Shorter Vertical Leg for Sanitary Steam Traps, BioPharm International, September 2006. http://www.biopharminternational.com/.

Pietro Perrone is a Proposals/Projects Manager at Millipore Corporation. He has a degree in chemical engineering from Tufts University with 20+ years purification/separation technology experience in process development/optimization, equipment scale-up, and project management.

Industry News In Brief

by Patti Charek

Biogen Idec Opens Incubator

Biogen Idec has a cadre of talented scientists working feverishly to discover breakthrough drugs. Over the years, the Cambridge biotech has also made acquisitions, established a $105 million venture fund, and licensed promising technologies to build a pipeline of potential life-saving therapies. Now, Biogen Idec is trying a new approach: setting up an incubator to help biotech start-ups get off the ground by providing them with funding, technical expertise, and office and laboratory space near its Kendall Square headquarters. "We felt we needed to pursue another mechanism" to support early-stage companies, said Rainer Fuchs, executive director of the Biogen Idec Innovation Incubator.

As the biotech revolution matures, Biogen Idec and other companies are trying to find creative ways to get in on the ground floor of promising research developed outside their laboratories. A few, like Biogen Idec, are setting up corporate incubators. Pfizer recently committed to spending up to $10 million a year on a new biotech incubator in La Jolla, CA, near San Diego, and is considering setting up another incubator in MA or another biotech hot spot. In addition, Genzyme said it is considering stepping up investments in young companies or setting up an incubator of its own.

Meanwhile, Fuchs said Biogen Idec hopes to house up to four or five companies in its biotech incubator within two years. But he said it's important to find good matches. He said the company sifted through more than 100 ideas before settling on Escoublac, founded by Columbia Medical Center professor Gerard Karsenty, who has found links between bone biology and metabolism. The company hopes to pioneer new treatments for patients suffering from type 2 diabetes and obesity, which have been on the increase in the US. Fuchs said Biogen Idec plans to give each company in its incubator between $3 million and $10 million in seed funding over several years, dedicated office and laboratory space, administrative support, and technical expertise. In return, Biogen Idec will receive stock in the companies and an option to eventually buy the rest at a prenegotiated price. (Source: Todd Wallack, The Boston

Globe, 19 December, 2007)

Vertex Pharmaceuticals Plans Deal with Harvard to Fund Research Projects
Vertex Pharmaceuticals plans to strike an unusual deal with Harvard University to fund research projects related to cancer, infectious diseases, and other areas Vertex is interested in - with few strings attached. Vertex said Harvard researchers will be able to publish their results freely and retain the rights to any technology they develop - something barred by some corporate research funders. Even so, Vertex chief executive Joshua Boger said he hopes the project will help his company begin a "dialogue" with Harvard researchers working in areas that could be useful to Vertex's development efforts. He said the company has already received dozens of proposals and decided to fund five of them, starting next year, committing a total of several million dollars over three years. If Harvard decides to license any technology developed, Vertex said it has the option to license it first. (Source: Todd Wallack, The Boston Globe, 19 December, 2007)

Bristol-Myers Squibb Agrees to Sell Billerica Unit
Bristol-Myers Squibb said it will sell its medical imaging unit in Billerica to private equity firm Avista Capital Partners for $525 million. The deal comes two weeks after Bristol-Myers said it would put the unit up for sale as part of a broader restructuring plan which includes cutting 4,300 workers worldwide, closing more than half of its manufacturing plants, and exploring selling other divisions. Bristol-Myers already cut 132 jobs at the Billerica unit this year. But Don Kiepert, who will run the unit for Avista after the deal is completed next month, said Avista is optimistic about its growth potential. "Even with a generic competitor . . . it's a very solid business," Kiepert said.

The medical-imaging unit, which also makes other products used in diagnostic procedures, has 800 employees, including 400 in MA. Kiepert said Avista, which has offices in Houston and New York, has no plans to reduce the head count or move operations out of Billerica. (Source: Todd Wallack, The Boston Globe, 18 December, 2007)

Lacking Definitive Offers, Biogen Idec No Longer for Sale
Biogen Idec is taking down the "for sale" sign. The company said it has decided to remain independent after failing to receive a single offer to buy the company. But it wasn't for lack of trying - over the past two months, Biogen Idec said, it had contacted every major drug company to see if any were interested in submitting a bid. "We ran a comprehensive and thorough sale process," spokeswoman Naomi Aoki said. "In the end, we didn't receive any definitive offers to purchase the company." The news is likely to relieve anxious employees, who were worried about what would happen in the event of a sale. Biogen Idec, founded on the cusp of the biotech revolution in 1978, has 4,300 workers, including 1,750 in Massachusetts.

Biogen Idec insisted its future remains bright as an independent company. It recently predicted revenue will increase by 15 percent a year and profits per share will jump by 20 percent a year through 2010. "The board emphasized that Biogen Idec's business strategy is working and generating strong operating and financial performance," the company said in a statement. (Source: Todd Wallack, The Boston Globe, 13 December, 2007)

Millennium's Cancer Drug May Prove to be a Blockbuster
Millennium Pharmaceuticals' only drug on the market, Velcade, is shaping up to be a potential blockbuster. Shares in the Cambridge biotech's stock recently hit a three-year high after Millennium reported surprisingly robust sales for the cancer drug. Analysts say doctors are increasingly relying on Velcade to treat two types of cancer, multiple myeloma and mantle cell lymphoma. Millennium recently estimated US sales alone will grow 20 percent this year, to $265 million, higher than initially expected. And a Cowen & Co. analyst, Rachel McMinn, predicted in a research report that US sales will probably climb to $420 million by 2009. McMinn predicted international sales will increase from roughly $500 million in 2007 to $921 million in 2009, giving Velcade well over the $1 billion in annual worldwide sales used to define a blockbuster in the pharmaceutical industry. Though Millennium sells Velcade in the US only, its partner Johnson & Johnson sells the drug in more than 85 other countries and has provided Millennium with a steady stream of royalties and other payments.

Velcade is part of a class of drugs called proteasome inhibitors, which block key processes in cancerous cells and cause them to die. Traditionally, it has been used to treat myeloma only after first trying other treatments. But Millennium presented data from 20 trials at the annual American Society of Hematology conference showing the drug

is effective as a front-line treatment for multiple myeloma. The company is also testing Velcade's effectiveness in treating other types of cancer, such as non-Hodgkin's lymphoma. Still, Velcade faces plenty of competition, including CelGene's Revlimid. In addition, at least two drug makers, Proteolix and Nereus Pharmaceuticals, are in the early stages of developing next-generation proteasome inhibitors that could compete with Velcade in the future.

Millennium, founded in 1993, now has a stock market value of close to $5 billion, making it one of the biggest biotech companies in Massachusetts. It has 960 employees, including 850 in the state. (Source: Todd Wallack, The Boston Globe, 10 December, 2007)

Japan's Eisai to Buy MGI Pharma for $3.9 Billion
Eisai Co Ltd said it would buy U.S. biotech firm MGI Pharma Inc for $3.9 billion in cash to strengthen its cancer pipeline, marking the largest overseas acquisition by a Japanese drugmaker. The deal is the latest example of accelerating M&A in the biotech sector, which has seen a scramble by big drugmakers to secure promising technologies and pipelines developed by smaller firms. It is a bold step by Eisai, which has yet to bring any of its own cancer drug candidates to market, to increase its foothold in the fast-growing cancer drug business and its international presence.

The nation's fourth-biggest drug firm said the deal would ensure growth in the U.S. market after the patent on its main earnings driver, Alzheimer's treatment Aricept, runs out in 2010. It also comes after a major setback for an experimental medicine for Parkinson's disease, which failed to meet its key goal in a late-stage trial. "To tackle these issues, management has moved flexibly and quickly, and the first impression is positive," said Kumi Miyauchi, analyst at the Daiwa Institute of Research. "With this purchase we can be very confident of achieving our goal of 440 billion yen in sales in the U.S. by March 2012 and 1 trillion yen in sales overall," Chief Executive Haruo Naito told a news conference. (Source: Edwina Gibbs, Reuters, 10 December, 2007

Sirtris Describes Three New Antiaging Drugs
The quest for antiaging drugs took another step as Cambridge-based Sirtris Pharmaceuticals described new chemicals that mimic some of the beneficial effects of a low-calorie diet in laboratory mice and rats. The company is a long way from helping humans live longer, but has seen some success with mice: in a scientific paper Sirtris co-founder David Sinclair described how laboratory mice fed a high-calorie diet lived an average of 20% longer if they also took a chemical called resveratrol. That attracted much attention and led to Sirtris's $62 million initial public offering in early 2007.

The company stresses that it wants to treat the "diseases of aging," such as diabetes, Alzheimer's and cancer, not aging itself, which the FDA doesn't recognize as a disease. Right now, Sirtris is testing high doses of resveratrol as a treatment for diabetes in a study of 130 people in India. Resveratrol, a naturally occurring substance found in low quantities in red wine, affects many different mechanisms in the body, including a protein called sirtuin enzyme one, or Sirt1. When fed a low-calorie diet, the body makes more of Sirt1 - and seems to ward off disease better and live longer. Sirtris believes that prodding Sirt1 to be more active will produce the same benefits without needing to cut calories.

Several companies, including Swiss pharmaceutical giant Novartis AG and Sirtris's crosstown rival, Elixir Pharmaceuticals, are studying Sirt1, but Sirtris says it is the farthest along. "We know that calorie restriction and exercise induces sirtuin activity in humans," said Christoph Westphal, Sirtris's chief executive. "We know we're mimicking this natural process." In the recent study, published in the journal Nature, Sirtris described three new drugs that supercharge Sirt1 without affecting other mechanisms. Like resveratrol, the new chemicals lowered the blood sugar of obese and diabetic-like laboratory mice and rats, supporting the notion that Sirt1 is important for defending against diabetes.

Sirtris highlighted that its new drugs are far more potent than resveratrol, meaning it can use smaller-sized pills and lower doses. But the new drugs still are much less potent than an existing diabetes drug, GlaxoSmithKline's Avandia, meaning they require higher doses to have the same effect. For Sirtris, the new chemicals have an added benefit - the company can patent them. Although Sirtris has several patents related to sirtuins and has more pending, the company can't patent resveratrol itself, which occurs naturally and is sold by several companies as a dietary

supplement. (Source: Keith J. Winstein, The Wall Street Journal, 29 November, 2007)

Pfizer to Buy Coley for $164 Million
Pfizer, one of the world's largest drug companies, is gaining another toehold in Massachusetts. The New York pharmaceuticals giant said it will buy Coley Pharmaceutical Group, a Wellesley biopharma, for $164 million. Coley has 115 employees, including 45 in MA. Pfizer already has about 150 employees at a research facility in Cambridge and says it plans to add more in the coming year. In addition, the company is considering opening a biotech incubator in the Boston area to complement an existing one near San Diego.

Pfizer said it was interested in Coley's vaccine technology to treat cancer and other diseases, as well as several experimental drugs designed to work by blocking key immune system receptors. Coley chief executive Robert L. Bratzler said the company has a promising pipeline of potential drugs, but needs money to continue development. Its most advanced experimental medicine, a cancer vaccine called VaxImmune, is at least five years from hitting the market and generating revenue for the company. By becoming part of Pfizer, Bratzler said, Coley should have the resources to carry on with its development work. He said Pfizer has proved to be an excellent partner over the past two years. (Source: Todd Wallack, The Boston Globe, 17 November, 2007)

Regulatory & Legislative Highlights

By Deepen "DJ" Joshi

FDA Approves First-of-its-Kind Drug for Treatment of Phenylketonuria (PKU)
The FDA has approved Kuvan (sapropterin dihydrochloride), developed by BioMarin Pharmaceuticals of Novato, CA in partnership with Merck Serono, the first drug of its kind approved to slow the effects of phenylketonuria (PKU). PKU is a rare genetic disorder that causes mental retardation, smaller brain size, delayed speech and other neurological problems. In January, 2004 Kuvan first received orphan drug designation; in January, 2006 it received a fast track designation and its new drug application (NDA) received priority review by the FDA based on its potential to offer a significant advantage to patients over current treatment options.

Kuvan works by increasing PAH enzyme activity in PKU patients with some residual PAH enzyme function. This then leads to an increased breakdown (metabolism) of phenylalanine (Phe), resulting in lower levels of Phe in the blood. Kuvan must be used in combination with a phenylalanine-restricted diet. A patient can override the effects of Kuvan by not following a Phe-restricted diet. Patients being treated with Kuvan must have their blood phenylalanine levels monitored frequently by their physicians or other health care professional. (Source: FDA Web site, 13 December, 2007)

FDA Launches E-mail Alert Subscription Service via Public Web Site
The FDA has announced a new e-mail service that alerts subscribers whenever information is updated on certain FDA Web pages. The service is free and available for a wide variety of FDA's Web pages, including food safety protection, medical product approvals and consumer health information.

"Being able to directly communicate with consumers, health care professionals and the regulated industry about the safety of our food supply and medical products is critical to FDA's ongoing commitment to protecting the public health," said Andrew C. von Eschenbach, MD, Commissioner of Food and Drugs. "E-mail is the leading use of the Internet, and this service strengthens FDA's ability to keep its audiences informed quickly and effectively."

To receive e-mail alerts, subscribers need only click on the red envelope icon located on participating Web pages. Each e-mail update includes a direct link to the FDA Web page that has been updated. Powered by GovDelivery, a private sector e-mail subscription management system used by several other federal agencies, the service allows subscribers the flexibility to personalize the information most important to them. A full list of currently available topics can be found at www.fda.gov/emaillist.html). (Source: FDA Web site, 3 December, 2007)

FDA Approves Nexavar for Patients with Inoperable Liver Cancer
The FDA has approved Nexavar (sorafenib) for use in patients with a form of liver cancer known as hepatocellular carcinoma, when the cancer is inoperable. Nexavar, a type of anticancer drug called a kinase inhibitor, was originally approved in 2005 for the treatment of patients with advanced renal cell carcinoma, a form of kidney cancer. It interferes with molecules that are thought to be involved in chemical messages sent within cancer cells, in the formation of blood vessels that supply tumors, and in cell death.

According to the National Library of Medicine, hepatocellular carcinoma accounts for 80 to 90 percent of all liver cancers. This type of cancer can be difficult to remove completely using surgery. If all of the cancer cannot be removed, the disease is usually fatal within three to six months. The American Cancer Society estimates that there will be 19,160 new cases and 16,780 deaths from cancer of the liver and intrahepatic bile duct in the United States in 2007.

Nexavar is manufactured by Bayer HealthCare AG of Leverkusen, Germany for Bayer Pharmaceuticals of West Haven, CT and by Onyx Pharmaceuticals of Emeryville, CA. (Source: FDA Web site, 19 November 2007)

FDA Announces Steps to Improve Advisory Committee Processes
The FDA is announcing several steps to strengthen its advisory committee processes in ways consistent with recommendations of the Institute of Medicine. The measures include proposed new procedures on advisory committee voting and disclosure of information on conflicts of interest. Both are described in recently issued draft guidance documents. Other improvements include improvements to the agency's advisory committee Web site, which can be found at http://www.fda.gov/oc/advisory/default.htm.

The first draft guidance document recommends advisory committees adhere to a process of simultaneous voting, in which all members vote at once. The results of the vote would be announced immediately. How each member voted would be part of the public record. The draft guidance document is available at http://www.fda.gov/oc/advisory/votingguidance.html.

The second draft guidance document lays out recommended changes to the process of public disclosure of financial interests that create conflicts of interest for advisory committee members. The new draft guidance makes the process more transparent and consistent by having all advisory committee members publicly disclose interests for which a waiver is granted. The draft guidance document and redesigned templates are available at http://www.fda.gov/oc/advisory/waiver/ACdisclosure1007.html.

FDA's policies on advisory committees continue to be informed by new studies on conflicts of interest. The agency asked a consultant, Eastern Research Group, to study 16 recent advisory committees. The report highlights the difficulty of assembling highly qualified experts who are free of conflicts and finds that those who have received waivers appear to be significantly more qualified than those who have not received waivers. The full report is available online at http://www.fda.gov/oc/advisory/ERGCOIreport.pdf.

In addition, FDA has improved its Web page on advisory committees by providing better access to information about waivers granted for conflicts of interest. This Web page provides current information about upcoming advisory committee meetings and other updated information related to FDA's advisory committee processes. The Web site is at http://www.fda.gov/oc/advisory/default.htm.

Finally, the FDA has recently posted the names of outside experts that it has named to a new risk communication advisory committee to make recommendations to FDA about how best to communicate the risks and benefits of FDA regulated products. More information about this advisory committee and the list of members can be found at http://www.fda.gov/bbs/topics/NEWS/2007/NEW01739.html.

So far this year the FDA has convened 47 meetings of expert independent advisory committees to advise the agency on topics such as new gene therapies and the safety of children's cough and cold medicines. (Source: FDA Web site, 15 November 2007)

FDA Adds Boxed Warning for Heart-related Risks to Anti-Diabetes Drug Avandia
The FDA has announced that GlaxoSmithKline (GSK), the manufacturer of Avandia, a drug used to treat type 2 diabetes, has agreed to add new information to the existing boxed warning in the drug's labeling about potential increased risk for heart attacks. Glaxo agreed to a "black-box" warning that says an analysis showed Avandia "to be associated with an increased risk" of ischemic events such as heart attacks, in which blood is choked off from the heart. However, the new warning also says the overall data are "not conclusive." GSK is also developing a Medication Guide for patients to provide additional information about the benefits and risks and safe use of Avandia.

At this time, FDA has concluded that there isn't enough evidence to indicate that the risks of heart attacks or death are different between Avandia and some other oral type 2 diabetes treatments. The previous upgraded warning emphasized that these types of drugs may worsen heart failure, a condition in which the heart does not adequately pump blood, in some patients.

To date, no oral anti-diabetes drug has been conclusively shown to reduce cardiovascular risk. Consequently, the agency also will be requesting that labeling of all approved oral anti-diabetes drugs contain language describing the lack of data showing this benefit. (Source: FDA Web site, 14 November 2007 and Anna Wilde Mathews and Jeanne Whalen, The Wall Street Journal, 15 November 2007)

FDA Strengthens Warning Labeling for Erythropoiesis-Stimulating Agents (ESAs)
The FDA recently approved revised boxed warnings and other safety-related product labeling changes for erythropoiesis-stimulating agents (ESAs) Epogen, Procrit and Aranesp. ESAs are a bioengineered version of a natural protein made in the kidney that stimulates the bone marrow to produce more red blood cells. Epogen, Procrit and Aranesp are approved to treat anemia in patients with chronic kidney failure and anemia caused by chemotherapy in certain patients with cancer. Epogen and Procrit are also approved for use in certain patients with anemia who are scheduled to undergo major surgery to reduce blood transfusions during or shortly after surgery and for the treatment of anemia caused by AZT therapy in HIV patients. Epogen, Procrit and Aranesp are manufactured by Amgen of Thousand Oaks, CA. Procrit is marketed and distributed by Ortho Biotech of Bridgewater, NJ, a subsidiary of Johnson & Johnson.

For patients with cancer, the new boxed warnings emphasize that ESAs caused tumor growth and shortened survival in patients with advanced breast, head and neck, lymphoid and non-small cell lung cancer when they received a dose that attempted to achieve a hemoglobin level of 12 grams per deciliter (g/dL) or greater. The boxed warnings also emphasize that no clinical data are available to determine whether there is a similar risk of shortened survival or increased tumor growth for patients with cancer who receive an ESA dose that attempts to achieve a hemoglobin level of less than 12 g/dL.

For patients with chronic kidney failure, the new boxed warning states that ESAs should be used to maintain a hemoglobin level between 10 g/dL to 12 g/dL. In addition to the boxed warning, the new labeling provides specific instructions for dosage adjustments and hemoglobin monitoring for chronic kidney failure patients who do not respond to ESA treatment with an adequate increase in their hemoglobin levels. (Source: FDA Web Site, 8 November, 2007)

FDA Requests Marketing Suspension of Bayer's Trasylol
The FDA recently announced that, at the agency's request, Bayer Pharmaceuticals has agreed to a marketing suspension of Trasylol, a drug used to control bleeding during heart surgery, pending detailed review of preliminary results from a Canadian study that suggested an increased risk for death.

FDA requested the suspension in the interest of patient safety based on the serious nature of the outcomes suggested in the preliminary data. There are not many treatment options for patients at risk for excessive bleeding during cardiac surgery, thus FDA is working with Bayer to phase Trasylol out of the marketplace in a way that does not cause shortages of other drugs used for this purpose.

Until FDA can review the data from the terminated study it is not possible to determine and identify a population of

patients undergoing cardiac surgery for which the benefits of Trasylol outweigh the risks. Two weeks ago, FDA was notified that researchers with the Ottawa Health Institute stopped a study on Trasylol because the drug appeared to increase the risk for death compared to two other antifibrinolytic drugs used in the study. Antifibrinolytic drugs help slow the breakdown of blood clots and subsequent excessive bleeding. (Source: FDA Web Site, 5 November, 2007)

FDA Approves Novartis' Tasigna for Treatment of Chronic Myeloid Leukemia
The FDA has approved Novartis' Tasigna capsules for treatment of Philadelphia chromosome positive chronic myeloid leukemia (CML) in adult patients whose disease has progressed or who cannot tolerate other therapies that included Gleevec. (Gleevec is approved for the treatment of newly-diagnosed patients with Philadelphia chromosome positive CML.)

CML accounts for 15 percent of all leukemias in adults, with approximately 4,500 new cases of CML diagnosed in 2007. FDA's approval of Tasigna includes a black box warning for possible life-threatening heart problems that may lead to an irregular heartbeat and possible sudden death. (Source: FDA Web Site, 30 October, 2007)

FDA Approves New Uses for Eli Lilly's Evista
The FDA has approved Eli Lilly's Evista tablets for reduction of the risk of invasive breast cancer in postmenopausal women with osteoporosis and in postmenopausal women at high risk for invasive breast cancer. Evista is associated with an increased risk of deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis. An increased risk of death due to stroke was observed in a trial in postmenopausal women with documented coronary heart disease or at increased risk for major coronary events. In addition, women should be aware that Evista does not completely prevent breast cancer and that regular mammograms and breast examinations are essential. (Source: FDA Web Site, 13 September, 2007)

Court Ruling May Stall Opening of Boston University Biolab
The state's highest court delivered a victory to opponents of a controversial research laboratory being built by Boston University, upholding a lower-court decision that cast doubt on whether the project will open on time next year. The project, known as the National Emerging Infectious Diseases Laboratories represents a bid by BU to vault into the top tier of the nation's medical research institutions. Underwritten by federal funds, the laboratory is a cornerstone in the Bush administration's campaign to prepare for potential acts of bioterrorism.

In a unanimous decision, the Supreme Judicial Court agreed that the state's environmental approval of the South End lab, granted by the Romney administration, was "arbitrary and capricious." The SJC also concurred that BU must complete another environmental review of the project and submit it to the state for approval.

The decision does not halt construction of the facility, already 70 percent complete, but does call into question when or whether BU will receive the permits necessary to open the centerpiece of the building: a Biosafety Level-4 lab where scientists will be able to work with the world's deadliest germs, including Ebola, plague, and anthrax. (Source: Stephen Smith, The Boston Globe, 14 December, 2007)

FDA Panel Votes Against Use of Genentech's Avastin to Treat Breast Cancer
The FDA advisory panel told the agency Genentech's blockbuster Avastin shouldn't win approval to treat advanced breast cancer, a blow to company efforts to expand the market for the drug. Avastin is approved in the US for use in forms of colon and lung cancer and in Europe as a breast-cancer treatment. The FDA typically follows the recommendations of its expert panels, however the panel's vote in this case was closely split , 5-4. Genentech wants to market Avastin as a first-line treatment for patients with recurrent or metastatic breast cancer based on a study sponsored by the National Cancer Institute.

The NCI study compared patients taking Avastin in combination with Taxol to those taking Taxol alone and showed an apparent advantage for Avastin in terms of "progression-free survival." However patients taking Avastin did not live significantly longer overall. The agency also said there were more safety issues among the patients taking Avastin. FDA officials said they believed six deaths were likely or clearly tied to the drug regimen in the Avastin patient group. The agency attributed no deaths to Taxol taken alone; Genentech officials said this number wasn't

clear because of how the study's data were collected.

The panel's deliberations highlighted an issue that could have broader implications: how to measure, and weight, progression-free survival. There has long been debate over what evidence is needed to prove that a cancer drug works if it hasn't clearly helped patients live longer. (Source: Anna Wilde Mathews, The Wall Street Journal, 6 December, 2007)

AstraZeneca's Nexium Clears FDA Hurdle
The FDA said a review of clinical studies involving AstraZeneca's drugs Nexium and Prilosec doesn't show an increase in heart attacks and sudden death. Both drugs are approved to treat gastroesophageal reflux disease, while Prilosec is also approved in an over-the-counter version marketed by Procter & Gamble to treat frequent heartburn.

The agency has been conducting a safety review of the drugs since May. At that time, AstraZeneca submitted the results of two small, long-term studies that suggested the drug could increase the risk of heart problems and sudden death. The FDA asked the company to submit additional information about the drugs for the FDA to review. The agency said its review of the studies shows the products are "not likely to be associated with an increased risk of heart problems." In a statement, AstraZeneca said it agreed with the FDA's conclusion. (Source: Jennifer Corbett Dooren , The Wall Street Journal, 11 December, 2007)

FDA Rejects Merck's Bid for Over-Counter Sale of Mevacor
For the third time, the FDA has rejected Merck's bid to sell the cholesterol drug Mevacor without a prescription, saying it wasn't clear that consumers would use the medication correctly. It is also a setback for GlaxoSmithKline, which has bought the US over-the-counter marketing rights to the drug.

Mevacor would have been the first statin sold over the counter if the FDA hadn't followed the advisory panel's recommendation to reject Merck's proposal. Statins, a class of cholesterol-lowering drugs, are the most frequently prescribed medicines in the US. Advisory panel members said patients need a doctor's help to determine whether they have high cholesterol and can take Mevacor safely. Newer and more powerful statins, which include Pfizer's best-selling Lipitor and Merck's own Zocor, now available generically, have long overtaken Mevacor in prescription use.

The regulatory record on over-the-counter switches is mixed. In the past, the FDA has allowed them for some drugs that treat obvious symptoms, including Schering-Plough's allergy medication Claritin and heartburn treatment Prilosec, marketed by Procter & Gamble; and Glaxo was able to overcome the agency's initial concerns about safety and consumer comprehension and win permission to sell the weight-loss aid Alli on drugstore shelves.

The agency is examining the possibility of a new regulatory category, called "behind the counter," which would allow pharmacists to dispense certain drugs without a physician's prescription. A few drugs are already effectively sold this way, notably the emergency contraceptive Plan B, which is only supposed to be provided to women 18 and older without a prescription. (Source: The Boston Globe, January 26, 2008; Anna Wilde Mathews, The Wall Street Journal, and Bloomberg News, both 14 December, 2007)

FDA Rejects Momenta Pharmaceuticals' Generic Version of Lovenox
The FDA rejected Momenta Pharmaceuticals' application to market a generic version of Sanofi-Aventis' Lovenox, a lucrative drug used to prevent blood clotting. The rejection is a surprising setback for Momenta, a promising biotech firm that had attracted an all-star team of backers and pledged to use new sugar sequencing technology to copy complex drugs, such as Lovenox, and create its own novel therapies.

For years, Momenta has been working to copy Lovenox with Sandoz, a unit of Swiss drug maker Novartis. Momenta said the FDA rejected its generic-drug application because the two companies didn't adequately address the possible impact of the drug on the body's immune system - a concern Momenta said regulators had not previously mentioned since Momenta and Sandoz filed an application for approval in 2005.

Teva Pharmaceutical Industries and Amphastar Pharmaceuticals have also been working on a generic version of Lovenox, but Momenta had been thought to be ahead in the race to reach market. Momenta executives also said they didn't know whether the FDA had similar objections to the generic drug applications filed by its rivals, or whether the companies had already answered the FDA's concerns in their applications. (Source: Todd Wallack, The Boston Globe, 7 November, 2007)

Abbott Stent Gets FDA Panel Backing Despite Clot Worries
Abbott Laboratories' move to expand its reach got a boost as an FDA panel backed the company's drug-coated heart stent, despite concerns about the long-term risk of causing blood clots. The panel of outside medical experts overwhelmingly said they believed Abbott's Xience stent was effective at propping open previously blocked cardiac arteries and said the scaffold-like device appeared to be safe for at least one year after being implanted. While most panel members said there simply wasn't enough data to address long-term safety issues, the panel voted 9-1 in favor of approving Xience for sale.

Drug-coated stents have come under fire for a tendency to cause life-threatening blood clots years after they are implanted in clogged arteries. It isn't clear whether the rare problem is caused by the metal stent itself, the drug that prevents the vessel from re- narrowing or the polymer that releases the drug. Sales of the two coated stents on the market, Boston Scientific's Taxus and Johnson & Johnson's Cypher, have sunk due to the safety concerns. (Source: Jennifer Corbett Dooren and Avery Johnson, 30 November, 2007)

Report Criticises Lack of Expertise at FDA: Says Staff, Funds are Inadequate
Lives are at risk because the FDA is woefully behind in the latest scientific advances and is under-funded for its vast responsibilities, according to a 56-page report titled "FDA Science and Mission at Risk." The report, commissioned by the FDA's chief and prepared by a subcommittee of the Science Board made up of specialists from government, industry and academia, indicates that inadequate staffing and poor retention, out-of-date technology, and a general lack of resources mar the agency's ability to do its job. Heightened scrutiny of the FDA in recent years stems from high-profile recalls of pharmaceuticals - including Merck's Vioxx, belatedly tied to increased risk of heart attack - and from its handling of food scares such as one involving tainted bagged spinach.

The report faults poor retention of critical employees, noting the turnover rate of the FDA science staff is twice that of other government agencies. It also notes lack of a good system of talking to scientists outside the agency, "thus limiting infusion of new knowledge and missing opportunities to leverage resources," and describes the panel as "extremely disturbed" at the state of the agency's information technology infrastructure, calling it the "weakest but most critical link." (Source: Kim Dixon, The Boston Globe, 4 December, 2007)

GlaxoSmithKline Cervical Cancer Vaccine Approval Delayed
The FDA dealt a blow to GlaxoSmithKline (GSK) in delaying approval of one of the company's most important new products, the cervical cancer vaccine Cervarix. The company said it received a "complete response letter" that the agency issues when the review of a drug or vaccine is completed and questions remain to be answered before approval.

GSK had been aiming to pit Cervarix against Gardasil, a rival blockbuster vaccine co-developed by Merck and Sanofi-Aventis with US sales exceeding $1.1 billion during the first nine months of 2007. While Cervarix and Gardasil protect against cancer-causing strains of the sexually-transmitted human papilloma virus, or HPV, they aren't identical. Gardasil targets four types of HPV, while Cervarix focuses on two strains that cause most cancer cases. Cervarix is formulated with an adjuvant that GSK says enhances the body's immune response and increases the duration of the protection. (Source: Elena Berton, The Wall Street Journal, 18 December 2007)

AstraZeneca's Crestor Gets New FDA Approval
AstraZeneca said its cholesterol-lowering drug Crestor has been approved in the US for the treatment of atherosclerosis, a move that could help diversify the product. The company said the FDA approved Crestor, as an adjunct to diet, to slow the progression of

atherosclerosis in patients with elevated cholesterol. Atherosclerosis is the progressive buildup of plaque in the inner walls of arteries. Last year, Crestor was AstraZeneca's third-best selling drug, with sales of more than $2 billion. (Source: The Wall Street Journal, 12 November, 2007)

New Members

Mr. Luke T. Almeida, New England Electropolishing

Ms. Monica J. Cahilly, GMQA, LLC

Ms. Virginia Corbin, Waters Corporation

Mrs. Jayna Dinsmore, Dakota Systems Inc.

Mr. Nick Dowd, Mettler-Toledo Thornton

Mr. Todd Griffith, CRB Consulting Engineers

Ms. Chris Heleter, Wyeth Biopharma

Mr. Simon M. Huang, University of New Hampshire

WheYong Lo, Copley Pharmaceutical

Padmadhar R. Madupu, Bristol Myers Squibb

Mr. Gary J. Mills, UMass Med School MassBioLogics

Mr. John Neroth, IN USA Inc

Mr. Stephen Perreault, Dakota Systems Inc

Cheryl A. Plummer, Wyeth Pharmaceuticals

Ms. Kimberly Riley, PhD, Shire HGT

Mr. Kevin J. Shield, DECCO Inc

Mr. Frederick Simard, Bristol-Myers Squibb

Mr. Michael J. Sommers, Trane

Ms. Kerry Spielberger, Acceleron Pharma

Leah K. Stidsen, Alkermes, Inc

Mr. Robert Swenson, Lonza Biologics Inc

Mr. Brian K. Warne, American Automation Inc.

Mr. David W. West, Genzyme Corp

Kenneth R. White, Richard White Sons,Inc

Donald Wuchterl, Shire, Human Genetic Therapies

Mr. Hossein Zarrin, MKS Instruments, Inc.

« 1 2 »

Chapter Manager: Amy Poole, CAMI - Tel: 1.781.647.4773 and E-mail: ispe@camihq.com