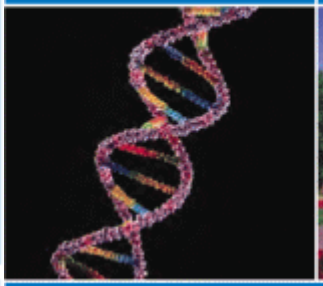
ISPE Boston Area Chapter
ENGINEERING PHARMACEUTICAL INNOVATION

www.ispe.org/boston




NEWSLETTER

August 2008, Volume XVIII, No. 4

Previous Issues

August 2008, Volume... (10)
June 2008, Volume... (11)
April 2008, Volume... (10)
February 2008, Volume... (10)
October 2007, Volume... (10)
December 2007, Volume... (13)

Newsletter Archive

Complete Facility Automation & Compliance Solutions for the Life Science Industry

GxP Automation

- Turnkey HVAC / Facility Automation
- GMP Monitoring / Process Integration
- Commissioning / Validation Services
- Technology Project Management
- UL508A Panel Fabrication Facility
- Rockwell Automation VFD Products

25 Mulberry Lane
Pelham NH 03076
(603) 898-6825

99 Hayden Ave. Suite 230
Lexington MA 02421
(781) 860-7900

www.GxPAutomation.com

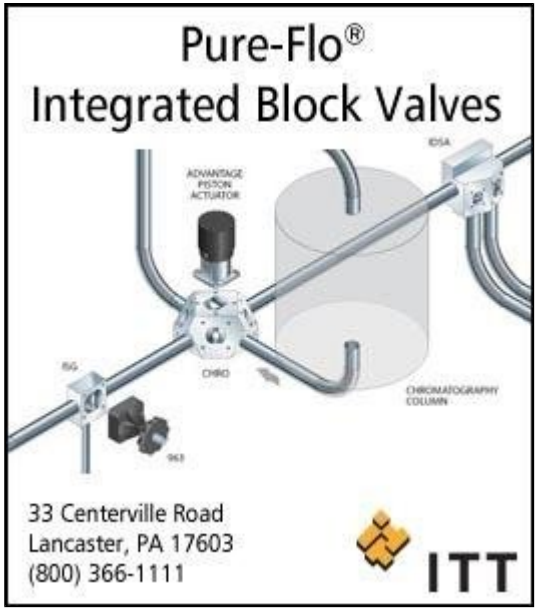
Return to the Table of Contents | Printing Instructions

Save page as PDF

President's Message: Who are the Top 20 ISPE Boston Area Member Companies?

Where does your company stand among the top 20 member companies of the ISPE Boston Area Chapter? Currently, the top companies and their corresponding members are:

1.	Genzyme	85
2.	Wyeth	82
3.	Shire	35
4.	Abbott Bioresearch Center	28
5.	AstraZeneca	27
6.	Alkermes	27
7.	Lonza	24
8.	Bristol-Myers Squibb	24
9.	Biogen Idec	22
10.	Parsons	20
11.	Siemens	18
12.	Millipore Corporation	17
13.	Mass. Biologic Labs	15
14.	Amgen	12
15.	Stryker Biotech	11
16.	Superior Controls Inc	10
17.	ImmunoGen Inc	10
18.	Eisai Research Institute	9



19. DECCO	9
20. Sepracor	9

With over 1300 individual members (up 12 percent this year) you can imagine how many companies are represented (exactly 437, plus six universities). If your company is not on the list above, you might want to ask your management, "Why not?" If you're a vendor, is your company truly committed to this industry? If you're a biotech or pharmaceutical manufacturer, are your people truly interested in manufacturing innovation and learning about new manufacturing, validation, and R&D methods?

There are many good business reasons to join and attend Chapter events. This past year, for example, the Boston Area Chapter has been extraordinarily successful. Nine exciting educational events, featuring a total of 23 expert speakers, were h eld in the Boston area. Four of these were sold-out, with standing room only. Coming up on September 16th at Genzyme's Cambridge facility, the hot topic of Six Sigma and how it can be applied to our industry will be presented.

In addition, this past year's events included two jam-packed networking events (our New Year's celebration and recent Summer Social and brewery tour - yes, we learned about fermentation), a ski trip to New Hampshire and of course there's the Golf Outing on August 18th which is sold out every year and has been for 10 years.

Finally, New England's largest one-day biotech event, the "ISPE Boston Area Product and Educational Show" will be held on October 8th this year, again in the indoor Club Seat Section (those are the expensive seats and restaurants) at Gillette Stadium. Be sure to attend this free event, enjoy the food, take a tour of the home of the Patriots (*almost* the four-time Super Bowl winners - we're so close!), visit the 275 product and service companies displaying their wares and enjoy one of the eight educational programs that will be offered. Last year there were over 1600 attendees and this year we expect more.

There are many reasons people are joining the Boston Area Chapter. The 20 companies listed above certainly know that membership for their employees is a very valuable way to reward and enhance their careers. And of course, it's fun.

I'd like to close by noting that my term as the Boston Area Chapter President will be coming to an end this summer and this will be my last President's letter. One year has gone by so fast. This experience has been incredibly exciting and enjoyable and I want to sincerely thank the Chapter's Board of Directors and all the committee volunteers that have helped in so many ways. I am grateful to so many and I feel I've made some life-long friends.

Proudly accepting Committee of the Year awards are
Dave MacDonald, Co-Chair of the Educational Program
Committee, and Janet Tice, Chairperson, and Chris Ciampa,

both of the Communications Committee.

Specifically, Doyle Johnson, your current Vice President and candidate for next year's President, has helped a great deal with the Product Show and so many other activities, always ready to pitch in wherever he is needed. The Past Presidents, especially Mike Denault and Dave Novak, have been an enormously valuable resource to call on. Some of the Committee Chairs of the most active committees, like Dave MacDonald and Mark Sitcoske (Educational Programs), Janet Tice (Communications), Sylvia Beaulieu (Social), and Brian Hagopian (Product Show) have spent many days of their free time coordinating events for your benefit. It's truly been a pleasure for me to have worked with the entire Board this past year.

Have a great summer and I look forward to seeing many of you at the August 18th Golf Outing and the October 8th Product and Educational Show.

Sincerely,

Rick Pierro

President, ISPE Boston Area Chapter

Upcoming Chapter Events - Mark Your Calendar

Monday, August 18, 2008
Annual Golf Outing
Ferncroft Country Club, Middleton, Massachusetts

Thank you to our 2008 Golf Tournament Sponsors!

- CRB Consulting Engineers
- DECCO
- GxP Automation, LLC
- Integra Companies
- Invensys Validation Technologies
- Steris Corp
- StructureTone
- Superior Controls

This year we have sold out the golf foursomes, however there is still room at our Networking Luncheon. Please join us for lunch and networking after the golf outing. The Cocktail Hour will start at 1:30 pm with the Lunch Reception to follow. Forms must be received by August 11th. The cost is $ 75 per person. If you are interested just call the office at (781) 647-4773.

Tuesday, September 16, 2008
Six Sigma Part II
Key to Efficient Innovation & Cost Effective Manufacturing Process
Genzyme Corporate Center, Cambridge Massachusetts

Speakers:
Philip Ramsey, North Haven Group
Philip Werth, Wyeth BioPharm

Click here for full information and to download a registartion form -

NRG
Providing Massachusetts Licensed Boiler Operators to the Pharmaceutical Industry
Let NRG Manage Your High-Pressure Boiler Systems
NRG Services, Inc
76 Webster St. - Worcester, MA 01603
508-767-1200 fax: 508-767-1300

SPEC
Process Engineering & Construction, Inc.
[ENGINEERS WHO BUILD]
"Let us solve your problems, no matter how big or small"

Engineering, Design, Build & Startup Services
Rapid Project Completion
Performance-based Contracts
17 A Street · Burlington MA 01803
www.spec-eng.com · sales@spec-eng.com · (781) 221-0123

http://www.ispe.org/galleries/boston-files/Sept-16-2008-Program-Flyer.pdf

---

Wednesday, October 8, 2008
Annual Product Show
Gillette Stadium Clubhouse, Foxborough, Massachusetts

Registration will open soon!

Click here to view a list of the Exhibiting Companies -
http://www.ispeboston.org/exhibitors/index.html

Water, Water Everywhere at May Educational Program

by David MacDonald

The topic of water - a topic that always draws a crowd - returned to the educational program of the ISPE Boston Area Chapter on May 20, 2008. The room at the Royal Sonesta in Cambridge was filled with members who had turned out to hear two of the area's long time experts (each with 20+ years experience) discuss this ubiquitous but complex topic. The first speaker gave a wide-ranging overview of purified water: types, specifications, contaminants and contaminant removal techniques, while the second explored the use of ozone as a technique to produce purified water and maintain good biological control.

The topic of purified water never fails to attract a record turnout and the May 20th educational program was no exception.

Brian Hagopian, Vice President of Research and Development for MarCor Purification, spoke first. His was a daunting challenge, covering "Water Purification 101: From Tap to Pure, Understanding the What, Why and How" in less than an hour. Hagopian quickly demonstrated his enthusiasm for his topic and his high skill as an educator, keeping the entire room with him during the whirlwind tour of the subject. The talk covered three areas. First, "What contaminants are found in water?" - second, "Which of these contaminants must be removed and why?"- and finally, "What are the basic technologies for removing these contaminants?" Interlaced with the technical discussion were many humorous asides, keeping the room light and the audience alert.

The basic groups of contaminants discussed were suspended solids, dissolved salts, low molecular weight organic materials, high molecular weight organic materials (also known as colloidal materials), bacteria (and other biological contaminants) and dissolved gases. Each class of contaminants has its own properties and requires differing approaches for removal.

Hagopian then raised the issue of why we should care about water contaminants and which contaminants need to be removed. The simple answer is that water is the most abundant single ingredient coming into contact with our products. It

Does Automation Technology Change?

ALWAYS!

Superior Controls is a leader in providing automation and information systems to the BioPharma Industry. We have the resources to meet your automation needs and our highly experienced engineers are attuned to the nuances of FDA validation requirements and the latest technologies available.

After All, Change is Exciting.

www.superiorcontrols.com 1-800-639-1736.

SUPERIOR CONTROLS, INC.

Trusted Automation Excellence

TEK STAINLESS PIPING PRODUCTS

The premier source for Biopharmaceutical components for your compliance with cGMP, validation, ASME BPE and USP Class VI requirements.

- BPE fittings and tubing
- In-house custom sanitary hose assemblies
- Class VI gaskets, tubing & molded products
- Diaphragm and ball valves
- Pressure and temperature instrumentation

SERVICE • EXPERTISE • INVENTORY

208 High St., Randolph, MA 02368
800-249-9337 • sales@tekspf.com
Visit us online at www.tekspf.com

is the carrier fluid in the vast majority of the pharma / biotech processes. Reducing the variability of pure water quality increases the repeatability and robustness of these processes. The second simple answer is that there is a long list of organizations (led by FDA and USP) that say that we will control the quality of water used in pharmaceutical operations.

Then there was a quick review of specifications for various grades of water. The FDA is mainly concerned with two types of Pharmaceutical Grade Water: USP Purified and USP WFI. Hagopian compared these two grades versus semiconductor grade water. The comparison was eye opening, with semiconductor grade having many more specifications and much tighter limits. And semiconductor grade water is routinely produced in high volumes.

The next topic was a survey of the technologies used for contaminant removal. For particles, the technologies include (in order of increasing fineness) particle filters, membrane filters, ultra filtration and reverse osmosis. Salts are removed by ion exchange, small organics by carbon filters and bacteria by UV sanitizers or TOC-reducing sanitizers. Distillation is the gold standard as it removes the water from its contaminants and the heat effectively kills all the bacteria.

Hagopian concluded by reviewing the largest local problem contaminants. These are the seasonal turnover in the local surface water supplies and the low molecular weight organic contaminants present in many public water sources. In closing, we were reminded that this was just the very basics of purified water, barely scratching the surface of a vast and complex subject.

Bob Livingston, President of Arion Water, was the next speaker, on "Best Practice for the Use of Ozone in Life Science Applications." This talk started with an introduction to using ozone as a key part of the water purification system and then presented some real life case studies. Livingston's thesis is that ozonation is an attractive choice to replace heat shock and chemical sanitization in high purity water production. Ozone is especially useful in improving the microbiological aspects of purified water production.

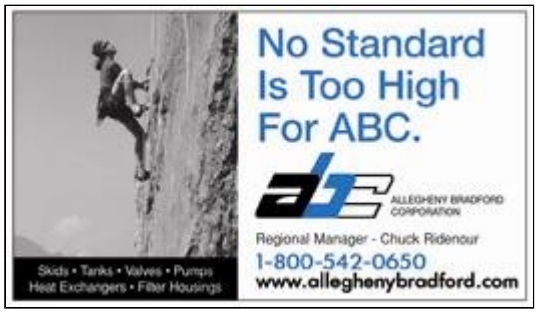
Livingston noted that purified water is too often conducive to microbiological growth. The relatively high limits on TOC and conductivity specified by USP Purified Water can support the growth of biofilms in the water production and distribution systems. Biofilm is a thin layer of bacteria and organic matter that occurs under the viscous boundary layer, at the interface between the bulk water phase and the solid system components, such as piping, filters and resins. Typically biofilms are kept under control in pharmaceutical water systems by the use of periodic heat or chemical sanitization cycles. Heat sanitization will control the growth of biofilms but will not completely remove existing biofilms. In comparison, semiconductor purified water systems operate at ambient conditions without heat sanitization cycles. Instead, they use nutrient deprivation as their control strategy. In extremely nutrient deficient environments, bacteria will not attach to surfaces. If the bacteria don't attach, they won't form biofilms in the distribution loop or elsewhere.

Ozone can be added to the water production system and /or the water storage and distribution system. Ozone serves two purposes. First, it is very effective at killing a wide range of microbial actors including spore forming species. It is orders of magnitude more effective as a sanitant than chlorine. Second, it can be used to remove the TOC contaminants of purified water through oxidation. Livingston stated that you can't get control of the microbiological aspect of purified water until you get high purity (and low TOC) in the distribution system.

In one case study, a 500-gallon DI water system had been idle for 6 years. When the system was restarted, the bacteria count was too high to measure. Ozone was injected into the water and in less than a day the TOC was reduced to < 5 ppb and the bacteria count was <1 CFU/100 ml. In a second case study, an operating system of good design produced water with acceptable TOC and bacteria counts for 14 months. The system still exhibited build up of biofilms and started showing periodic bacteria excursions. The system was modified to use ozone to reduce and control the TOC level. By reducing the TOC level to < 2 ppb, the bacteria count was reduced to < 10 CFU/100ml with no excursions, without the use of chemical sanitization. When Livingston stated that ozonated water cleans out existing biofilms, light bulbs went on over the heads of many in the audience.

Livingston then briefly reviewed the choices for ozone manufacturing methods, means for dissolving ozone in the water and destroying the residual ozone. When introducing ozone into a water system, use of the appropriate materials of construction is one key. Another key consideration is the need for online measurement of effective ozone level control. There has been recent progress in this measurement.

Ozone has been used for intermittent sanitization of distributions loops, passive microbial control via TOC reduction and routine process sanitization. One key point is that there is a need to rinse the use points with ozonated water to keep them sanitized. One real advantage of ozone sanitization is that is creates no additional wastewater and doesn't leave a residue



which must be cleaned from the system before use.

The speaker's conclusion is that TOC control - at levels well below that required for USP Purified Water - is essential to the good operation of a DI water system. And ozonation is an effective treatment for reducing TOC and bacteria counts and removing biofilms.

Both speakers' presentations are available for members at the ISPE Boston Area Chapter web site at www.ispe.org/boston/events.

ISPE Washington, DC Conference - Education, Networking and Lots of Fun!

by Rick Pierro
Photographs by Doyle Johnson

It's entirely appropriate that the ISPE Annual Regulatory Compliance Engineering Conference be held right outside the nation's Washington DC capital. After all, that's where the FDA big wigs hang out and they don't have to go very far to give fabulous talks on regulatory trends and issues for the 500 or so ISPE delegates that gathered from across North and South America this past June 2-6.

Educational talks were well attended, with delegates coming from Canada to Brazil to hear the latest updates on topics like the following:

- Science and Ri sk-based Approach (for C&Q): Application of the New Guide, Installation and Verification (In Support of ASTM E2500);
- Regulatory Perspectives on Hot Topics, Regulatory Trends, and Observations;
- Application of the New Risk-MaPP ISPE Baseline® Guide GAMP® 5: Enabling Innovation and Technological Advance.

Rick Pierro and Miguel Perez Colon of the Puerto Rico Chapter took the opportunity to share information (as well as dinner) during the Conference.

But interesting educational talks were not the only things brewing at the Conference. Approximately 80 of the nation's top vendors participated in the table top show; 17 national committee meetings (COP, Education, Member Services, Student Development, Regulatory Affairs, etc) were held; and representatives from 15 ISPE Chapters met together for a full 8-hour day (16 hours if you include our networking event) to exchange ideas, best practices and discuss plans for the future.

The Boston Area Chapter was well represented at these meetings with Doyle Johnson (Vice President), Mike Denault (Past President) and Rick Pierro (President) attending the North American/South American Affiliate Council (NASAAC) meeting, In addition, Dave Novak headed up the Membership Services Committee and presented the results to the entire NASAAC.

But the best part, as always, were the networking events. This is often where the deals are made, ideas are hatched, and friendships are formed and the Washington Conference was no exception. For example, the Boston Area Chapter representatives took the Puerto Rico Chapter leaders out for dinner one night and learned all about ISPE in the Caribbean, discussed regulatory requirements with the Argentina Affiliate and chatted about European business growth with the United Kingdom Affiliate. By the time the week was over, many of the delegates, myself included, were already looking forward to the next Conference to be held in Boca Raton, Florida in October!

Chapter leaders turned out in force for the ISPE North American/South American Affiliate Council (NASAAC) meeting in DC.

A Successful ISPE Summer Social Proves All Is Well in the Boston Area Chapter

by Christopher Ciampa
Photographs by Rick Pierro & Chris Ciampa

Beer, laughter, commotion, talk about the biotech and pharmaceutical sectors: What do these things have in common? They are just some of the sights and sounds that took place during the Boston Area Chapter's Summer Social at Boston Beer Works on June 11th. The gathering started at around 6pm on the second floor of the Canal Street facility. Owner companies, large and small, as well as a vendors, suppliers and consultants to the industry were all well represented. What better way to network with an impressive group of people who work in the life science industry? And better yet, as a thank you for their participation in the Chapter, the event was free for Members!

Speaking of impressive, the room on the second floor we had set up for us was phenomenal. It had an area with cozy chairs, dinner tables for 10 or more people, plus a few pool tables for those who are pool players. Throughout the evening there were plenty of hors d'oeuvres and entrées available. The food included salad, chicken tende rs, buffalo chicken strips, pork dumplings, steak tips, mashed potatoes, green beans, rice and more. Of course, for drinks attendees enjoyed an assortment of the brewery's homemade lagers and ales. (I personally tried a Belgian white ale [it looks like Budweiser beer and has that beige/tan color], which was very smooth and pleasing to the palate.)

At about 6:20, our fearless Beer Works tour guide, Dennis, began our tour of the brewery. He knew we would be a tough crowd: pharmaceutical folks, who, to his thinking, were well-versed in chemistry and biology. Because of this, he asked people to bear with him (or "beer" with him, however you want to look at it) while he attempted to explain the process of making beer to people who were biotech-savvy.

The beer-making process begins by storing the malts in a grain silo. Specialty malts (to give beer characteristics such as color, flavor, and body) are added to

the grain silo, and the malts are weighed out and run through a roller mill (to gently crush the grain into grist). The entire amount of malt for a single brew is then stored in the grist case. Next, the malt is transferred to a mash tun, where the malt mixes with hot water to become mash. It rests in the mash tun for an hour while enzymes convert the malt starch to fermentable sugars. Later, there is a sparging process, in which the grains are rinsed with water and the resulting liquid (now referred to as "wort") drained into the "brew kettle."

The June 11th Summer Social provided members with food, drink and conversation in a relaxed setting.

Interested members were treated to a 30-minute tour of the brewery operation during the Summer Social.

In the kettle, the wort is boiled for an hour and 15 minutes and varying amounts of hops are added to give bitterness, flavor, and aroma characteristics. After the boiling process, the wort needs to be prepared for fermentation, so a counter-flow heat exchanger (using glycol and city water) is used to cool it down to 65°F. Oxygen is also infused into the wort at this point to help with yeast respiration.

Next, the fermentation process that we have all been waiting to read about takes place Here, yeast mixes with the cool and aerated wort; the process usually takes about six hours to initiate. Once it does take place, the yeast utilizes fermentable sugars to create alcohol and carbon dioxide. To make ale, this process takes 3 to 6 days at 70°F and for lagers, about 7 to 10 days at 52°F. After the initial fermentation takes place, a secondary fermentation follows in a closed "conditioning" tank. For beer, this process takes two weeks at 45°F and for lagers, four weeks at 38°F. As Dennis reminded us at the end of the tour, "Brewers don't make beer; they simply provide the right conditions so the yeast can make beer." Beer is "beer" once the yeast has fermented the wort.

Once the conditioning process is completed, the beer is cooled to 35°F, filtered and then transferred to dispensing tanks. The beer can be served from the dispensing tank or it can be put into kegs. And of course, the final (and most important) step is to drink and enjoy!

Later in the evening, Boston Chapter President Rick Pierro gave a toast to the Chapter's members. He said that the Boston Chapter has grown 13 percent in the past year! He also presented one of two "Committee of the Year" awards to the Communications Committee and congratulated Chairperson Janet Tice and the Committee for their good work over the past year (The second award was presented to Dave MacDonald and the Educational Program Committee at an earlier event.). Next came a raffle sponsored by: A-Z Corporation, M.A. Olson Co., Particle Measuring Systems, Plastic Concepts and the Chapter. Gifts ranged from Red Sox tickets to gift certificates to fancy Boston restaurants!

All in all, the Summer Social was a huge success. Many thanks to Amy Poole, Rick Pierro, Doyle Johnson, and Sylvia Beaulieu and the entire Chapter Board of Directors for making this event possible and for making it a memorable one! "Beer's" to you!

Members felt right at home with The Boston Beer Works stainless steel tanks providing a backdrop for the Chapter's Summer Social.

You Want it When?!?

by Joseph A. Naughton
Photographs by Doyle Johnson

If you've ever wondered how in the world you're going to get your MVR done in time to get the FDA to approve your HPH2Os, CDAs, and CEs as scheduled, you might want to hear what these experts had to say about phasing your C&Q and building your BOD to finish PDQ and report more ROI to your CEO!

Over 100 of ISPE's finest gathered at the Royal Sonesta Hotel in Cambridge on June 17, 2008 to catch up with fellow industry professionals and to engage in some light conversation focusing on challenges and solutions in merging quality and facility requirements with accelerated schedules, the never ending desire to change the plan once it's set, and the pressure to get on line faster. Leading the discussion were two of the region's seasoned facilities implementation and validation gurus: Michael Marino and Charles E. Pappalardo. They spoke at both the micro and macro scales about

common challenges and solutions to relieve the pressure and reduce the temperature the process often involves.

Mike began the discussion with a presentation titled "Controlled Environment Commissioning and Qualification: Using a Phased Approach to Meet Schedule Demands." The setup is as follows: For virtually every project there is a firm construction schedule and a firm manufacturing startup schedule, and stuck in the middle is the Commissioning and Quality (C&Q) system process, which would be fine except for what Mike refers to as the C&Q "squeeze" factor. The C&Q squeeze typically results from construction delays pushing the construction finish out and/or operational pressures that pull the manufacturing start date in. The net effect is that C&Q typically gets squeezed into an increasingly narrow crevice of time between the finish of construction and the start of manufacturing activities. To deal with this recurring challenge, Mike recommends a phased approach to C&Q. The phased approach is designed to document and execute a logical and defendable Qualification Plan (QP) to commission, certify and qualify Controlled Environments (CEs) and systems that saves time by synchronizing simultaneous construction and C&Q activities. This synchronized and simultaneous approach allows C&Q activities to start as individual systems are finished and turned over, as opposed to waiting until the entire construction process is complete before starting the C&Q plan. The way this works is as follows: The team must allow the qualification process to be split up into phases for each of the areas being constructed and generate, execute, and approve each document set as the individual systems comprising the project are turned over by the construction process. Of course all this synchronization and simultaneity sounds great but it can only happen by building the right plan which Mike recommends you lay out with a QP flow chart showing the major steps in the process including:

"You Want it When...?" drew over a hundred membersto the Sonesta in Cambridge on June 17th.

1. Defining the roles and responsibilities for each team member;
2. Identifying the specific team players including a third party commissioning team;
3. Developing the project quality scope including a task list with durations and assignments;
4. Formalizing multiple Master Validation Plans (MVPs) that document in detail the scope of each qualification with acceptance criteria; and
5. Establishing systems boundaries for the MVPs and C&Q plans.

Once the structure is set, you can advance your C&Q plan with the commissioning component. The commissioning process starts with the development and approval of a Design Intent Document (DID) that goes to a third party commissioning company as early on in the design and construction process as possible. The DID should be structured to accommodate a parceled approach to approving building systems such as the HVAC system, building automation system, and pure water system, to name a few. The plan should be integrated into the design phase with agreed-upon formats for reporting well in advance of construction (synchronized) in order to reap the time-saving benefits of simultaneity mentioned above.

The Qualification process starts with the development of an "all-encompassing" quality plan that documents the phased approach and establishes multiple MVPs for each of the individual systems approvals. The MVP is usually the first document read by the Qualification auditor, which is why it needs to describe in detail what you're going to do and include the "why rationale." The MVP should also describe at what point in the qualifications process manufacturing can begin.

Qualification requirements are organized into Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ) categories. The IQs should cover the as-built conditions for your Controlled Environments

(CEs) and related systems including High Purity Water (HPH2O) and Clean Dry Air (CDA) to name a few. The IQ is a formal verification that the rooms were installed as designed and working properly with respect to temperature, humidity, particulates, etc.

Upon approval of the IQ, the room or system is ready for the OQ review. The OQ is a verification that the CEs and related systems and critical utilities are operating over time as required by the MVP. The OQ includes static tests

Reflecting "at rest" conditions as well as dynamic tests on a 24-hour/5-day operation capturing the "in operation" conditions and any variation. Upon successful retest and approval of any corrective measures or deviation remediation, the OQ is approved and the CE and related systems can be released for process validation runs (though not in-human use manufacturing) and the PQ stage.

The final qualification, the PQ, is intended to test the "routine" operation of the CE and related systems and usually involves a minimum of 2-3 manufacturing weeks and/or 2-3 lots worth of product. Once again, following any corrective action needed, retest and approval, the PQ is approved for the given system. The qualification results for the IQ, OQ, and PQ are summarized in a Master Validation Report (MVR) that identifies any failures and resolutions, system acceptance documentation, and which is approved by the auditor, and the CEs and systems are released for in-human manufacturing. Another benefit of the phased approach is that it can be planned at the front end to accommodate "staggered" manufacturing process validations at the back end.

Chapter Members Jay Zaino and Sylvia Beaulieu prove that ISPE educational programs can be enjoyable as well as informative.

It should be noted that while the phased approach is a good shock absorber to C&Q squeeze, it also often results in more paperwork to "stitch" the parcels together in the documentation for the MVR. Mike indicated a threefold increase in paperwork should be contemplated when using this time-saving but more documentation-intensive approach. Clearly the C&Q process leading to a successful validation is onerous, but using the phased approach can help take some of the pressure and heat out of the "squeeze."

Following Mike's in-depth view of the validation process, Chuck took a step back and focused his discussion on the larger issue of moving a project quickly from concept to completion in a presentation titled "Accelerating Advanced Infrastructure Delivery." He began by outlining some of the most commonly voiced challenges facing the prototypical development project. These include the need to:

...have it yesterday,
...cut the budget,
...comply with the regulations but keep it "flexible,"
...make major changes to the program when you're pouring concrete,
...understand that every end user is "Customer #1,"
...keep multiple team members "in the loop,"
...minimize maintenance,
...maximize product production,
...get to market now, and
...keep quality job number 1.

While there is no perfect solution to such a complicated process with as many variables as you will find in your every day biopharm development project, there are some key measures that, when carefully applied, will make the process move much more smoothly and ensure a higher degree of success: Based on his own experience, Chuck outlined the following success factors:

- Stressing the importance of team coordination,

- Achieving an early integration of key stakeholders,
- Developing comprehensive programming up front,
- Setting realistic budget expectations,
- Setting credible schedule expectations, and
- Driving execution.

Team coordination starts with appropriate prequalification and selection of critical consultants to assure that the team chemistry is balanced and the necessary areas of expertise are well covered. In a market where every consultant is trying to win every commission, prequalification is critical to prevent an inadvertent "perpendicular" selection to a specific project need.

The team process also needs to be well defined and consistently visible in meeting notes, action items, gate keeper logs, accountability, critical dates, and milestones. The gate keeping process is the structure that allows the team to rigorously track changes to the project plan after a program or Basis of Design (BOD) has been approved by the project's key stakeholders. The log provides a formal presentation and reflection record of team decisions that may have both short-term and long-term impacts. The log will show, for example, that a conscious team decision was made to change the chiller plant from two 1,500 ton chillers to three 1,000 ton chillers to achieve operational redundancy, even though it cost more money and could take more time to complete. The log keeps the entire team involved and the project memory current. This brings us to the next critical component which is the early integration of key stakeholders.

The early integration of key stakeholders and functional experts during the BOD process will increase internal project support, maximize scope capture from the outset, and provide for an "all in" BOD. Key stakeholders should include representatives from Quality, Validation, Engineering, OPS, Facilities, IT, Security, R&D, Procurement, and Real Estate departments in addition to end users. And by having an "all in" BOD, the chances for establishing a truly realistic budget and schedule are maximized.

The BOD process, also referred to as programming, generally represents about 2 percent of the total project cost for a facility. The BOD derives from the strategic plan and typically results in a physical space program describing the types and sizes of spaces contemplated for a particular capital asset, with concept design and specification defining the basic scope of the project. Key stakeholders, designers, planners and cost estimators should be integrated into this process to confirm that needs are adequately identified and project costs including design, construction, furniture, equipment, land and financing are covered by the BOD.

This information is then packaged and used to develop return measurements, such as Return on Investment (ROI), Net Present Value (NPV), Internal Rate of Return (IRR) and Payback, for presentation to management and the request for a "go- no go" decision. As stated above, the BOD typically represents about 2 percent of the project cost, so if the response is a no-go, your risk is limited. If the response is a go, the next step is to refine the BOD and request the next level of funding for the Design phase which represents another 10-12 percent of project cost. This incremental approach to project funding requests is part of Chuck's approach to setting realistic budget expectations.

Setting realistic budget expectations can be promoted by first organizing the development process into three manageable slices of work effort and owner resource commitment:

1. The Basis of Design (BOD) or programming and concept development effort representing approximately 2 percent of project cost;
2. Design and preconstruction leading up to a Guaranteed Maximum Price (GMP) or "Bid," representing approximately 12 percent of project cost, and
3. Construction, commissioning and validation, representing approximately 86 percent of project cost.

By requesting approval for each of these phases incrementally, you avoid the potential to over commit owner resources and keep expectations within well defined limits. Upon approval of the BOD phase described above, the design and preconstruction phase can begin. This phase involves issuance of Request for Proposals (RFPs) and selection of a design team to prepare construction documents and produce the project performance specifications. Once again it is critical to integrate your key stakeholders into this process, as was done in the BOD phase, to assure a continuity of the

"all-in" support system and scope capture that will undergird your cost and schedule estimates.

Toward the end of the design and preconstruction phase, Chuck recommends utilizing the 80-100 percent complete design documents for inclusion in a Request for Proposal (RFP) to Construction Managers (CMs). The CM RFP is intended to solicit qualitative and quantitative proposals, including estimates for construction cost and schedule reflecting the BOD and current design. Upon receipt of the CM proposals, and often a third party check estimate, you will have the scope, cost, and schedule information, as well as stakeholder buy in, to make another financial presentation to management for your next "go- no go" decision. A positive response from management at this stage allows you to move into the construction commissioning validation phase that will bring the new facility on line.

Setting credible schedule expectations is akin to the discussion on programming and budget above, in that you will want to assure full integration of all support team schedules (Commissioning, Quality, Validation, Engineering, OPS, Facilities, Equipment, IT, Security, R&D, Procurement, and Real Estate, and Construction) in a master schedule prepared by the CM. This process, for example, can help to avoid the C&Q squeeze that Mike spoke of earlier, with construction commissioning, quality, and validation all integrated in the planning and implementation phases of the development. It is also important to revise the schedule regularly to accommodate any refinements or necessary adjustments that may require a recovery plan to maintain set milestones. A two-week look ahead is also recommended, and constant communication among the stakeholders is critical and can be encouraged by the use of a project FTP site to host project data.

Finally, driving execution of the plan relies on strong leadership, enforcement of accountability and measurement of key performance indicators (KPI) to gauge progress and make course corrections as necessary. Chuck recommends carefully interviewing critical team members such as the CM superintendents and project managers to ensure appropriate experience and team chemistry. Strong leadership will also benefit from periodic team building to maintain focus, direction, enthusiasm, and productivity. Enforcing accountability by each project team member is critical and can be done by penalizing low performance and rewarding achievement. Accountability also entails identifying team weaknesses and making changes and other corrective action early to maintain project momentum and efficiency. Finally, defining and measuring KPI in terms of schedule adherence, budget adherence and team coordination is critical to good project management.

Clearly the facilities development process, on both micro and macro scales, is faced with challenges that require careful advance planning to achieve positive outcomes. We can see how a phased C&Q plan is a great way to deal with the C&Q squeeze that so often occurs as construction dates are pushed out and manufacturing dates are pulled in. It is also helpful to know that these large endeavors can be effectively disaggregated into a smaller subset of tasks and incremental approvals to limit risk and better protect owner resources. When coupled with earlier involvement of key stakeholders, these tools allow us to build better solutions to strategic planning needs and report more ROI to the CEO!

Tech Talk: Scale-Up to 1000-Liter Perfusion Cell Culture in a Single-Use, Stirred-Tank Bioreactor

by Matt Niloff

Overview

Bioprocess scientists have long sought to expand the application of perfusion cell culture in order to achieve the theoretical productivity gains compared to batch and fed-batch approaches. The perfusion process is based on continuously adding nutrient solutions to the bioreactor while removing wastes from it. This keeps the organism in optimal growing conditions. However, this simple process presents practical challenges that often thwart those efforts.

Perfusion operations enable biologics manufacturers to achieve production volumes with smaller bioreactors which results in reduced capital costs and reduced footprint for the equipment. In some cases, smaller seed bioreactors can also be eliminated. Perfusion enables productive processing of unstable products by limiting the exposure of products to damaging proteases. Slow-growing or difficult-to-grow cell lines can often be productively grown only in perfusion operations.

The advent of bioprocessing based on single-use components is creating opportunities to broaden and simplify the use of perfusion, primarily due to the elimination of complex and time-consuming cleaning and sterilization steps, as well as the

reduction in the risk of contamination. Recent advances in the supply of single-use bioprocess equipment such as bag assemblies, bioreactors, mixing systems, centrifuges, and filter cartridges make implementation of single-use processes a feasible alternative to traditional biomanufacturing processes.

This article presents the results from the evaluation of a perfusion-based process utilizing single-use bioreactors, a single-use mixing system, and a single-use centrifuge. The combined operation of these systems permitted successful 1000L/day harvesting. The project resulted in successful development, scale-up and demonstration of a perfusion mode operation at the 200L (160L working volume) and 1000L scale using exclusively single-use process equipment. The 1000L process was operated for one month, with 12 harvests over 19 days, and was only terminated at that time as proof of concept had been achieved. The program concluded with a successful demonstration of process viability and reliability that exceeded the initial performance expectations.

Equipment Description

Equipment is shown in the Process Layout photo.

Bioreactor

Single-use bioreactor systems with nominal working volumes of 200 liters and 1,000 liters. These systems included the following components with associated features:

Single-use Assembly

— All product contact surfaces single-use except for sensors.
— No assembly required within sterile barrier.
— USP Class VI films & components, low endotoxin, low particulate, non-cytotoxic materials.

Bioreactor Hardware and Controls

— Turnkey, fully integrated system with jacketed vessel, integrated temperature control and process controller.
— Stirred tank design - bottom magnetic drive agitation with no rotating seals, integrated sparger with open pipe.
— 5:1 turndown ratio (systems able to operate at 20 percent of maximum volume).

The remainder of the perfusion train consisted of:

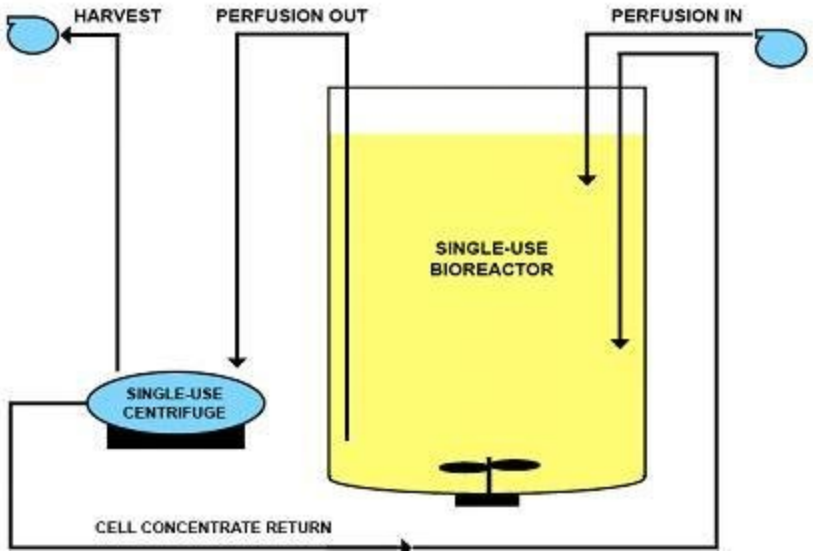
Media Prep System: Prototype 1000L media mixing system that produced 1000 liters/day.

Single-use External Cell Retention Device: Pneumatic Scale single-use centrifuge system.

Chilled Harvest Collection System: Chilled mixing/storage system.

Process Description

Cells were grown in a 1000L single-use bioreactor operating at 1000L working volume. The bioreactor was installed on a load cell to monitor system weight and was operated at a constant 1000KG. Supernatant was removed at a fixed rate and sent to the single-use based centrifuge. A concentrated stream of cells was returned directly from the centrifuge to the bioreactor, and the load cell/controller loop governed a pump that would add new media based on the system weight readings in order to maintain constant volume in the bioreactor.



The primary objective was to assess the advantages offered by a single-use based process, including:

- Very fast process setup
- No need for CIP/SIP
- Less space required
- Short turnaround time between batches
- Easy product changeover
- Facility flexibility

The criteria to determine success included:

- Bioreactor working volume: up to 1000 L
- High cell density: be able to reach 10 million cells/ml
- Product comparability
- Reliability: be able to support one-month process

The application evaluated was:

- Cell line: Human cell line
- Culture mode: suspension perfusion cell culture
- Media: animal-product-free media
- Perfusion rate: 1.0 v.v.d.

Results

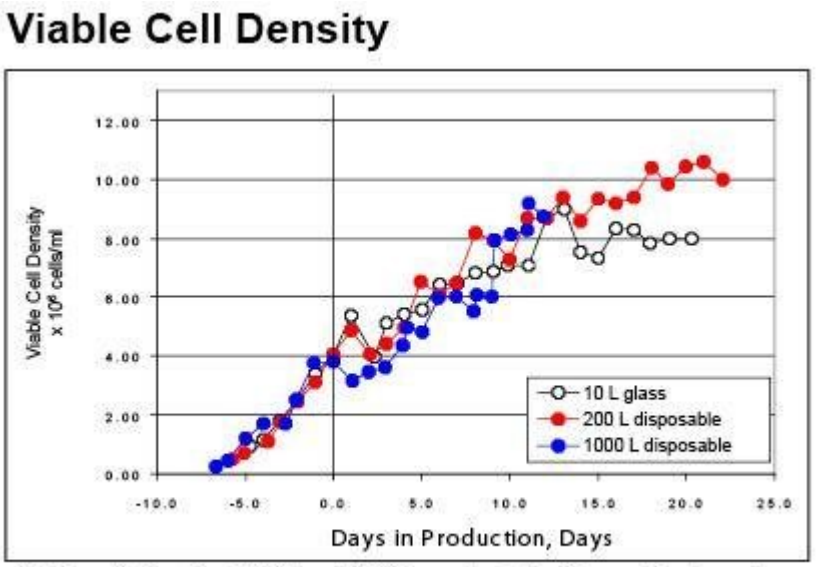
Process runs conducted:

10 L glass bioreactor run	27 days with 22 harvests

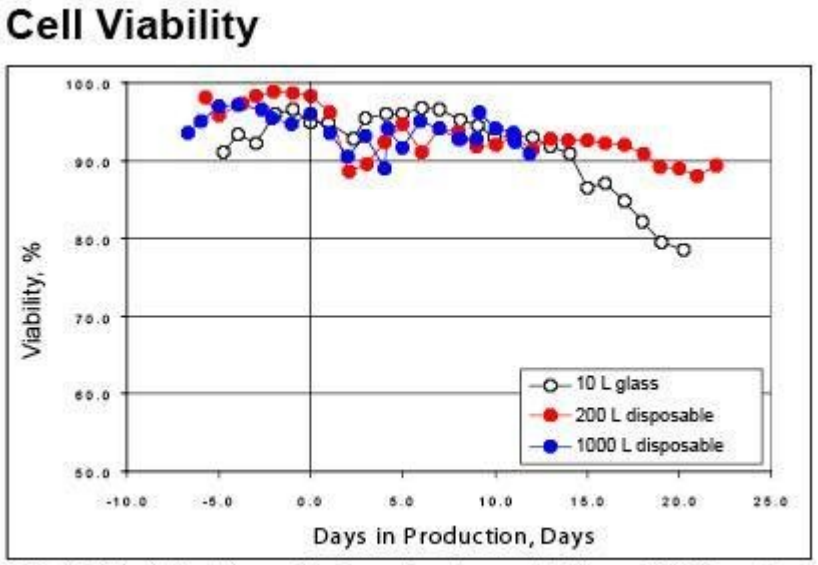
160 L single-use run	28 days with 22 harvests
1000 L single-use run	19 days with 12 harvests

The charts below illustrate the outcomes of the 1000L perfusion run compared with a 200L (at 160L working volume) run and a 10L bench-top run. The results demonstrate successful perfusion process scale-up and continual cell culture at 1000L as measured by cell density, cell viability, protein production/yield and other criteria. The process demonstrated equivalent control of:

- Temperature
- pH
- DO



Viable cell density at 200L and 1000L scale in the disposables-based systems were comparable to 10L benchtop performance



Cell viability in the disposables-based systems at 200L and 1000L scale were comparable to 10L benchtop

These results show the single-use based process delivered performance comparability of cell viability, viable cell density, and product yield (data not shown) at 200L and 1000L. The overall system reliability also exceeded expectations.

As the current trend in disposables expands throughout the industry, many bioprocess operations will continue to be simplified. Implementation of disposable technology in the process can result in reductions in footprint, set-up time, risk of cross contamination, capital costs, and operating costs. The example here for a perfusion-based process demonstrates the equivalent performance of single use disposable equipment at different bioreactor volumes. This flexibility along with the increase in protein titers and drug potency, are contributing factors to the potential that commercial-scale manufacturing at 2000L will be a reality in the near future for new therapeutics coming to market. Such a scale for disposable bioreactors is currently available.

About the Author

Matt Niloff is Senior Director of Products at Xcellerex, Inc., a leader in the development and deployment of innovative single-use bioprocessing technologies. Matt is responsible for Xcellerex's XDR line of single-use bioreactors and XDR and XTM single-use mixing systems. Prior to joining Xcellerex, Matt held various positions at Stedim Biosystems and Millipore Life Sciences. He also worked previously at the MIT Center for Genome Research on the Human Genome Project. Matt holds a Master of Science in Biology from McGill University. Matt can be reached at 508-683-2296 or MNiloff@xcellerex.com.

Regulatory and Legislative Highlights

By Deepen Joshi

Coronary Artery Plaque Imaging Device Cleared by FDA

The FDA has approved a device that a doctor can use to see inside a blood vessel to assess the fat content of the plaque which builds up on the wall of the coronary arteries. The device, called the LipiScan NIR Catheter Imaging System, is

manufactured by InfraReDx Inc. of Burlington, MA. The device is approved for use during cardiac angiography by physicians who are evaluating patients with symptoms of coronary heart disease.

Plaque is a deposit made up of cholesterol-rich fat, calcium, and other substances found in the blood. As plaque accumulates on the artery wall, it reduces blood flow to the heart muscle and increases the risk of blood clots which can lead to a heart attack. Nearly one million Americans suffer a heart attack every year and about half die. Many heart attacks occur when a fatty coronary plaque ruptures, forming dangerous blood clots.

The InfraReDx LipiScan NIR Catheter Imaging System works by placing a catheter equipped with a fiber-optic laser light into the artery. The device shines the near infrared light delivered through the blood to the artery wall, and measures the light reflected back from the artery wall, a technique called spectroscopy. The reflected wavelengths vary depending on how much fat and other substances are in the plaque in the illuminated portion of the wall. (Source: FDA Website, 29 April, 2008)

FDA to Fill More Than 1,300 Positions

The FDA is hiring hundreds of individuals with science and medical backgrounds to help meet the agency's responsibilities to assure the safety and/or efficacy of human and veterinary drugs, biological products, medical devices, food, cosmetics and products that emit radiation. In fiscal year 2008 alone, the FDA is looking to fill more than 600 new positions and to backfill over 700 others, nearly triple the number of people hired from 2005-2007. Qualified candidates could be on the job in as little as three weeks.

The critical need occupations are medical officers, consumer safety officers, chemists, nurse consultants, biologists, microbiologists, health/regulatory/general health scientists, mathematical statisticians, epidemiologists, pharmacologists, pharmacists and veterinary medical officers. Many of these positions are located in the Washington metropolitan area, specifically Rockville, Silver Spring and College Park, MD, as well as across the country in the FDA's five regions, 20 districts, more than 179 resident posts, and the newly created FDA offices overseas.

The FDA will be participating in and holding job fairs throughout the country. To find a job fair near you, visit http://www.fda.gov/jobs/jobfairs08.html. For general information and to apply for one of the positions listed above, submit your questions and electronic curriculum vitae with a cover letter via email at joinourteam@fda.gov. (Source: FDA Website, 30 April, 2008)

Manufacturer Removes Remaining Stocks of Trasylol

Bayer HealthCare Pharmaceuticals Inc. has notified the FDA that the company will begin removing the remaining stock of the antifibrinolytic drug Trasylol from the US market. Most of the remaining stock is in warehouses and hospital or physician's stock. The FDA will work with Bayer to ensure a smooth and complete process.

Results from a Canadian study prompted last November's marketing suspension of Trasylol. These results are expected to be published this week. The data suggest that Trasylol appears to increase the risk for death compared to two other antifibrinolytic drugs used in the study.

Under a limited use agreement, access to Trasylol is limited to investigational use of the drug according to the procedures described in a special treatment protocol. Trasylol is approved to reduce blood loss during surgery and the need for blood transfusion in certain patient undergoing cardiopulmonary bypass in the course of coronary artery bypass graft surgery. Antifibrinolytic drugs help slow the breakdown of blood clots and subsequent excessive bleeding.

The FDA has not yet received full study data from the study's researchers at the Ottawa Health Research Institute but supports Bayer's decision to completely remove Trasylol from regular use in the US market. FDA oversight requires comprehensive and thorough studies of a drug not only during the pre-market review phase but throughout the drug's life cycle. (Source: FDA Website, 14 May, 2008)

New Sentinel System to Help Improve Medical Products for Patient Safety and Quality of Medical Care

HHS Secretary Mike Leavitt has announced efforts at the FDA and the Centers for Medicare & Medicaid Services (CMS) that will complement each other to improve patient safety and the quality of medical care. The Sentinel System will be created through public-private partnerships and will capitalize on existing large electronic claims and medical records data sources maintained by private and government entities that agree to participate in this nationwide effort.

A CMS final regulation published today will make it possible for federal agencies, states, and academic researchers to use claims data from the Medicare prescription drug program (subject to protections for beneficiary privacy and commercially sensitive data) for public health and safety research, quality initiatives, care coordination and other research and analysis.

Creating an active surveillance system such as the Sentinel System was one of the recommendations made by the Institute of Medicine in a 2006 report on ways to improve the safe use of drugs. The recently passed Food and Drug Administration Amendments Act of 2007 (FDAAA) includes provisions that call for the development of such a system. As planned, the Sentinel System will fulfill some requirements of FDAAA while also meeting additional FDA needs. (Source: FDA Website, 22 May, 2008)

FDA Proposal Targets Labeling Information on the Use of Medicines during Pregnancy and Breast Feeding

The FDA has proposed major revisions to the physician labeling for prescription drugs (including biological products) to provide better information about the effects of medicines used during pregnancy and breast feeding. The proposed changes would give health care professionals more comprehensive information for making prescribing decisions and for counseling women who are pregnant, breast feeding, or of child-bearing age about using prescription medications.

The proposed rule outlines what information about the use of medicines during pregnancy and breast-feeding would be required to be added to product labeling for newly approved drugs. Under the proposal, drug labeling would explain, based on available information, the potential benefits and risks for the mother and the fetus, and how these risks may change during the course of pregnancy.

Current labeling uses a letter category system to describe the risks of drug use during pregnancy. The proposed rule would remove the letter categories and replace them with a newly designed format with three sections:

- The first section, called the "Fetal Risk Summary," would describe what is known about the effects of the drug on the fetus. The proposal calls for a risk conclusion based on the available data and provides a number of examples depending on the quality and quantity of that data.
- Another section, called "Clinical Considerations," would include information about the effects of the use of the drug if it is taken before a woman knows she is pregnant. This section also would feature discussions about the risks of the disease to the mother and the baby, dosing information, and tell how to address complications.
- The third section, under the heading "Data," would describe in more detail the available data regarding use of the drug in humans and from animal studies that were used to develop the Fetal Risk Summary.

The breast feeding section would use the same format and would provide information about using the drug while breast feeding, such as the amount of drug in breast milk and potential effects on the breastfed infant. Certain newly approved drugs would use the new labeling format, while labeling for previously approved drugs will be phased in gradually. (Source: FDA Website, 28 May, 2008)

FDA and European Medicines Agency (EMEA) to Consider Use of New Biomarkers When Assessing New Drug Safety

In the first use of a framework allowing submission of a single application to the two agencies, the FDA and the European Medicines Agency (EMEA) worked together to allow drug companies to submit the results of seven new tests that evaluate kidney damage during animal studies of new drugs. The tests measure the levels of seven key proteins or "biomarkers" found in urine that can provide additional information about drug-induced damage to kidney cells, also known as renal toxicity.

Development of the new biomarkers was led by the Predictive Safety Testing Consortium (PSTC), whose members include scientists from 16 pharmaceutical companies. The PSTC was organized and led by the Critical Path Institute, a nonprofit organization that works to support FDA research collaborations that improve the development of medical products. The consortium then submitted applications for use of the biomarkers to FDA and EMEA.

The project is the first in which a group of drug companies has worked together to propose and qualify new safety tests and then present them jointly to the FDA and EMEA for consideration. The new process allowed the PSTC to submit a

single biomarker data application to both regulatory agencies, and then to meet jointly with scientists from both agencies to discuss it in detail and to address additional scientific questions posed by the regulators. Each regulatory agency then reviewed the application separately and made independent decisions on use of the new biomarkers. (Source: FDA Website, 12 June, 2008)

Drugs Risk of Cancer Under FDA Scrutiny

US regulators are investigating a possible association between rheumatoid arthritis drugs made by Johnson & Johnson and Amgen Inc. and childhood cancer. The FDA found 30 cases of lymphomas in patients age 18 or younger who took anti-inflammatory drugs from a group that includes J&J's Remicade and Amgen's Enbrel, according to an "early communication" posted on the agency's website.

The FDA began investigating cancer cases linked to the class of medicines, known as TNF blockers, which also includes Abbott Laboratories' Humira, 10 years ago. The prescribing information for all of the medicines already warns of cancer risks. The family of drugs is approved to treat childhood rheumatoid arthritis and Crohn's disease, an intestinal disorder. Both diseases are caused by an abnormal immune response that attacks and damages healthy tissue.

J&J has provided additional data to the FDA and will be working "very closely" with the agency to answer their questions, said Michael Parks, a company spokesman. (Source: The Boston Globe, 5 June, 2008)

FDA Extends Review Period for Lilly Antiplatelet Drug Prasugrel

Eli Lilly has reported that the FDA has extended the review period for prasugrel, a potential blockbuster anticlotting drug, based on supplemental information provided during the review period. The three-month extension allows the agency the additional time it needs to complete its review. Prasugrel was granted priority review by the FDA in February 2008. The new FDA action date for prasugrel is September 26, 2008.

Prasugrel is being co-developed by Eli Lilly and Japan's Daiichi Sankyo for the treatment of patients with acute coronary syndromes (ACS) being managed with an artery-opening procedure known as percutaneous coronary intervention (PCI). In addition, a large Phase III clinical trial to compare the effects of prasugrel against clopidogrel (Plavix/Iscover) in medically managed ACS patients will begin shortly.

The new study in being conducted in conjunction with the Duke Clinical Research Institute (DCRI), the world's largest academic clinical research organization and a part of Duke University Medical Center. The study is a multi-center, double-blind, randomized, controlled trial to evaluate the safety and efficacy of prasugrel against clopidogrel in reducing the risk of cardiovascular death, heart attack or stroke in ACS patients who are to be medically managed without a planned artery-opening procedure.

Acute coronary syndromes, which comprises heart attacks and unstable angina (chest pain), affects more than 1.4 million people in the United States annually. Despite currently available treatments, 320,000 people experience recurrent heart attacks each year. Prasugrel works by inhibiting platelet activation and subsequent aggregation by blocking the P2Y12 adenosine diphosphate (ADP) receptor on the platelet surface. Antiplatelet agents prevent platelets from clumping or sticking together, which can result in clogged arteries and may lead to heart attack or stroke. (Source: Eli Lilly Website, 23 June, 2008)

Pharma Settlement Agreements Restrict Generics' Ability to Enter the Market

The Federal Trade Commission's Bureau of Competition has issued a summary of agreements filed with the agency in fiscal year 2007 by generic and branded drug manufacturers. Of 33 final settlements, nearly half (14 of 33) included both compensation to the generic company and a restriction on the generic's ability to market its product. "This report confirms that settlements with potentially anticompetitive arrangements continue to be prevalent," said FTC Chairman William E. Kovacic. "The Commission remains committed to ensuring that brand and generic companies do not use such settlements as a way to deny consumers the benefits of competition."

Commissioner Jon Leibowitz added, "... pay-for-delay settlements continue to proliferate. That's good news for the pharmaceutical industry, which will make windfall profits on these deals. But it's bad news for consumers, who will be left footing the bill. These agreements inflict special pain on the working poor and the elderly, who need effective drugs at affordable prices." (Source: Federal Trade Commission Website, 21 May, 2008)

EU Clears GlaxoSmithKline Bird Flu Vaccine

GlaxoSmithKline has announced that the European Commission has granted a marketing authorisation for its pre-pandemic H5N1 vaccine Prepandrix in all 27 EU member states. GSK is the first company to obtain a European license for a pre-pandemic vaccine, thereby offering European governments the potential for protecting their population in advance or at the onset of an officially declared influenza pandemic. "This vaccine marks a significant step in the world's ability to cope with an influenza pandemic," said GSK CEO Jean-Pierre Garnier.

According to the World Health Organisation (WHO), vaccines are the most important intervention for preventing influenza and reducing its health consequences during a pandemic. There are two vaccine-based approaches that could be used in the event of a pandemic - a pandemic vaccine and a pre-pandemic vaccine. Pandemic vaccines are produced as soon as a pandemic is declared, using the specific pandemic influenza strain. These vaccines will however, due to long manufacturing lead times, only be available four to six months after the onset of a pandemic, which will likely be too late for many of the victims of the first pandemic wave.

A pre-pandemic vaccine is produced in advance of a pandemic. Such a vaccine is based on the currently circulating avian H5N1 influenza virus likely to cause a pandemic and has the ability to raise immune protection against potential drift H5N1 strains. Pre-pandemic vaccines therefore play a critical role in pandemic preparedness planning, with experts citing that immunization with such stockpiled vaccines in advance or at the onset of a pandemic is the most effective strategy for protecting entire populations.

H5N1 influenza (often referred to as bird flu) infections can lead to severe disease in both birds and humans. To date, WHO has reported 382 human cases of H5N1 infection from 14 countries resulting in 241 deaths. Public health experts fear that this virus may evolve into a strain that is easily transmitted between people, triggering a worldwide pandemic. Influenza pandemics are global outbreaks that involve viruses, like H5N1, to which humans have little or no immunity.

GSK has previously announced its intention to donate 50 million doses of their pre-pandemic H5N1 vaccine to the WHO in support of its stockpile initiative. The donation would help establish a much needed stockpile of pre-pandemic vaccines that can be distributed to the world's poorest countries at short notice by the WHO. GSK has already signed contracts with the US and several European countries, such as Switzerland and Finland. (Source: GlaxoSmithKline Website, 19 May, 2008)

Bush Administration Proposes Additional $275 Million for FDA

HHS Secretary Leavitt has announced that the Administration is amending its budget request for fiscal year 2009 to include an additional $275 million for the FDA. He called on Congress to act quickly on this budget amendment and pending Administration legislative proposals to strengthen FDA. The budget request supports the fundamental change in strategy currently underway at FDA to adapt to the demands of the rapidly growing and changing global economy. These funds will expedite implementation of the strategy outlined in the Action Plan for Import Safety and the complementary Food Protection Plan, both released in November 2007.

"Last year we outlined important changes in how this nation deals with imports. We are moving from an intervention strategy -- where we stand at the border and try to catch things that are unsafe -- to an integrated strategy of prevention with verification. We are rolling the borders back and seeking to build safety and quality into products at every step of the way before they reach American consumers," Secretary Leavitt said.

Under the budget amendment, FDA will be able to expedite steps to improve import safety, including:

- establishing an FDA presence in five countries or regions and implementing other measures that will help ensure greater foreign compliance with FDA standards;
- offering expedited entry for goods bearing certification by trusted parties;
- modernizing its information technology infrastructure; and
- conducting at least 1,000 more foreign inspections of food and medical product facilities and an additional 1,000 domestic inspections.

The increase brings the Administration's total proposed increase in the FDA's budget for FY 2009 to $404.7 million -- a 17.8 percent boost in funding from FY 2008.

"FDA's mission to protect and promote the health of the America public will be greatly aided by these additional funds to implement our strategic plan," said FDA Commissioner Andrew C. von Eschenbach. (Source: FDA Website, 9 June, 2008).

Industry News in Brief

by Patti Charek

Governor Signs $1b Biotech Industry Benefit Plan

When the world's biggest biotechnology trade show opened in Boston last year, Governor Deval Patrick unveiled a bold proposal to pump $1 billion into the state's growing life sciences industry over the next decade. On June 16th, Patrick headed to this year's convention in San Diego to tell biotech executives he is finally delivering on that promise. After months of tweaking the plan, both the Senate and House ratified the final version of the bill. Patrick signed the legislation before jetting off to the annual BIO show, run by the Biotechnology Industry Organization trade group. The bill includes $250 million in tax incentives for companies, $250 million in grants, and $500 million for infrastructure, much of which is earmarked for the state university system. Several local biotech companies, including Shire, Genzyme, Wyeth and Organogenesis, stand to directly benefit from the legislation. Though biotech still only accounts for a little more than 1 percent of the state's workforce, Patrick has focused on nurturing the life sciences industry because of its growth potential, high salaries and ability to pump money into the economy.

Patrick said the legislation gives him a powerful platform to sell Massachusetts to biotech leaders-encouraging more companies to expand or set up shop here. The governor didn't head to California alone. Roughly four dozen state and local officials also attended, including House Speaker Salvatore DiMasi and Senate President Therese Murray, in an effort to promote the state's growing biotech industry. Massachusetts, along with San Diego and the San Francisco Bay area, is widely considered one of the top biotech clusters in the world.

More than 50 Massachusetts companies sent representatives to the annual BIO show, among them Vertex chief executive Joshua Boger (who is also the chair of the Biotechnology Industry Organization), Genzyme chief executive Henri Termeer and Jeff Elton, chief operating officer of the Novartis Institutes for BioMedical Research in Cambridge. (Source: Todd Wallack, The Boston Globe, 16 June 2008)

Sanofi Trumps Rival's Offer for Generic Drug Maker

The French drug maker Sanofi-Aventis said that it would offer about $2.5 billion for the Czech drug maker Zentiva, trumping a rival bid by PPF Group. The bid would take Sanofi deeper into the field of generic drug production, an area that has traditionally been shunned by large pharmaceutical companies but that is receiving increased interest as a way to tap emerging markets. Sanofi is already a major shareholder in Zentiva, with a 24.9 percent stake. PPF, in partnership with the Italian insurer Generali, holds a 19.2 percent stake in the company.

"Sanofi-Aventis is already established in the various markets where Zentiva operates," Sanofi said in a statement. "The intended acquisition of the control of Zentiva carries a strong strategic rationale." Milan Vanicek, an analyst at Atlantik FT, said that he did not believe PPF would accept Sanofi's offer. Vanicek said that PPF was likely to raise its own bid, either in an effort to gain control of the company or to prompt Sanofi to raise its bid.

Zentiva is a dominant supplier of generic drugs in the Czech Republic and Slovakia, and it also has subsidiaries in Romania and Turkey. The company said it had no immediate comment on Sanofi's counterbid. Zentiva told its shareholders to take no action for now on PPF's bid, saying it would call a shareholder meeting to discuss the offer. PPF said it would proceed in line with the terms of its own offer. The offer allows for a possible increase of its bid, but also for a withdrawal of the offer in case of a counterbid. (Source: Reuters, 19 June 2008)

Glaxo Vaccine Wins UK Contract

GlaxoSmithKline PLC said it won a three-year contract to supply the British government with its cervical cancer vaccine

Cervarix, marking an important win as Glaxo battles rival Sanofi Pasteur MSD for government vaccination contracts in Europe. Cervarix immunizes against strains of the human papillomavirus that cause most cases of cervical cancer.

Glaxo will sell Cervarix to the state health system for about $157 per shot. Each girl must be vaccinated with three shots. Britain's Department of Health aims to vaccinate all girls age 12 to 13 each year. Glaxo, based in Brentford, England, got regulatory approval to sell Cervarix in Europe in September. Sanofi-Pasteur MSD, a joint venture between Sanofi-Aventis SA of France and Merck & Co. of Whitehouse Station, NJ, got its rival vaccine, Gardasil, to the European market a year earlier and has won the business of several countries so far, including Switzerland and some regions in Italy, Spain and Sweden.

Eddie Gray, president of pharmaceuticals Europe for Glaxo said the company has won 16 government contracts in Europe so far. Glaxo estimates there are 20 million girls age 12 to 18 in Europe, making Cervarix a "significant opportunity" for the company there. (Source: Jeanne Whalen, The Wall Street Journal, 19 June 2008)

Eisai Closing MGI Pharma Cancer Lab in Lexington

Japanese drug company Eisai Co. Ltd. has informed 80 workers in Lexington that it plans to close its research facility there. News of the shutdown comes after more than a year of rapid growth at the facility, the site of its MGI Pharma subsidiary, where the number of scientists and support staff had swelled from 30 people to 80 people since early 2007. But plans have drastically changed at the R&D shop, which Eisai acquired as part of its purchase of Minnesota-based MGI for $3.9 billion five months ago. Eisai spokeswoman Suzanne Grogan did not say whether employees in Lexington would be offered jobs at other Eisai sites. She said the company may make further decisions about the Lexington operation in 30 to 60 days. "Everything's being evaluated and determined," Grogan said.

Eisai, which has US headquarters in New Jersey, employs about 225 scientists and other workers at Eisai Research Institute of Boston in Andover. Local executives suggested that MGI's research of cancer treatments, now in Lexington, could move there. MGI remains in operation at 35 Hartwell Ave., Lexington, and has recently vacated space it had leased at 44 Hartwell Ave., where life sciences firm Raindance Technologies Inc. of Guilford, CT plans to relocate. MGI began operations in Massachusetts following its 2004 buyout of Lexington biotech firm Zycos Inc. (Source: Ryan McBride, Mass High Tech, 16-22 May 2008)

Indevus Shares Plunge as FDA Requests More Information on Drug Candidate

Shares of Indevus Pharmaceuticals plunged after the Lexington company said its injectable testosterone drug candidate will face a regulatory delay of up to two years with the FDA because of safety concerns. Indevus said it expects the FDA to formally request additional safety data on Nebido before considering it for approval. Indevus will likely have to perform another study on the drug to get that data. The stock fell 69.5 percent, reaching its lowest point in nearly six years.

Indevus said it plans to refile its application with the FDA in about 18 months, followed by a six-month review. The FDA is concerned about a reaction seen in one patient immediately following injection of the drug, which led to coughing episodes and shortness of breath. In rare cases, symptoms from amounts of the oily injectable solution entering the vascular system can include dizziness, flushing, or fainting. The drug, which treats male hypogonadism, is already approved in Europe. Indevus said safety concerns likely arose from post-marketing studies conducted in Europe.

"We are very surprised and disappointed by the position the FDA is taking regarding the safety profile of Nebido, given the large European experience," Dr. Glenn L. Cooper, chairman and chief executive, said in a prepared statement. "Rare coughing reactions have been well-described in the European product labeling of Nebido." Indevus has 265 employees, including 115 in Massachusetts. (Source: Associated Press, 5 June 2008)

Glaxo Eliminating R&D Jobs as Part of Cost-Cutting Plan

GlaxoSmithKline PLC said it is cutting 2 percent of its global research and development staff, or 350 jobs, in another sign of the drug industry's struggle to stay profitable amid an increasingly tough business environment. The move is part of a cost-cutting program that Glaxo announced in October under the previous chief executive officer, Jean-Pierre Garnier. At the time, Glaxo said the cuts would save $1.37 billion a year by 2010 but didn't say how many jobs would be eliminated. Most big pharmaceutical companies have been laying off thousands of employees over the past year as their profits are squeezed by a variety of factors, including stiff competition from low-cost generic medicines and drug buyers' growing unwillingness to pay for expensive new drugs.

Glaxo is laying off employees at three research labs in the US, and in Britain and Italy. Before the cuts, Glaxo had 17,000 R&D staffers world-wide. The layoffs come as Glaxo's CEO Andrew Witty pledges to increase the company's investment in research happening outside of the company. In May, Glaxo said it was starting a venture fund to invest in early-stage technology or drugs that could provide the company either financial return or access to new products down the road. (Source: Jeanne Whalen, The Wall Street Journal, 12 June 2008)

Settling of Lipitor Patent Fight Protects $12b in Sales at Pfizer

Pfizer Inc. and India's Ranbaxy Laboratories Ltd. have agreed to keep copies of the cholesterol pill Lipitor off the US market an additional 20 months, protecting $12 billion in sales for Pfizer. Under a lawsuit settlement, Ranbaxy won't sell a generic version of Lipitor, the world's top-selling drug, until November 2011. Analysts had projected Ranbaxy would enter the market when the main patent expires in March 2010, though Pfizer sued to block it until 2016.

The deal buys Pfizer's chief executive, Jeffrey Kindler, time to find drugs to replace as much as $12 billion a year that's at risk when Lipitor copies reach the market. Pfizer, the world's biggest drug maker, has lost 32 percent of its value since Kindler took over in July 2006. "It is one of the most significant steps Kindler has made," said Michael Krensavage, president of Krensavage Asset Management in New York. "It clearly will enhance the value of the company..."

Pfizer and Ranbaxy have been fighting in US courts since 2003 over Ranbaxy's bid to sell generic Lipitor. Pfizer sued Ranbaxy again in March, this time over patents expiring in 2016 related to the process of making atorvastatin, the active ingredient in Lipitor. Pfizer has another patent on Lipitor that expires in 2017. The agreement ensures Ranbaxy can enter the market five years before patents on the process of making Lipitor expire without having to fight in court.

Pfizer has faced a string of setbacks since 2006, when it halted testing on the experimental cholesterol pill torcetrapib which had been positioned to replace Lipitor. Last year, the company stopped selling its inhaled insulin, Exubera, projected to have $1 billion in annual revenue. Sales of its antismoking pill, Chantix, have fallen almost a third since it was tied to suicides in January.

When a drug goes generic its sales typically fall as much as 80 percent because health insurers automatically switch their patients to the generic. Teva Pharmaceutical Industries Ltd., the world's biggest generic-drug maker, also is challenging the Lipitor patents in a case pending in Delaware. (Source: Bloomberg News, 19 June 2008)

Vertex Sells HIV Drug Royalty Rights for $160M

Vertex Pharmaceuticals Inc. has sold the rights to future royalties for two HIV drugs it helped develop for $160 million in cash. The Cambridge company sold to an unnamed investment entity rights to future royalties for both Lexiva and Agenerase. Vertex closed the deal under a 1993 license agreement it inked with GlaxoSmithKline PLC, which has been marketing the HIV drugs and paid Vertex royalties that started at 15 percent of sales. Vertex will use the money to help invest in key programs and future business initiatives.

Vertex brought in just over $34 million in royalty revenue from GSK in 2007 for its HIV treatments. The investment entity that purchased the future royalty stream declined to be identified. Vertex announced earlier this year that it would sell stock and convertible senior subordinated notes to raise up to $405 million to help support development of Telaprevir, its new treatment for hepatitis C. (Source: Boston Business Journal, 3 June 2008)

Novartis Targets Superbugs with Purchase of Drug Firm for up to $400 Million

Novartis AG has bought privately held Pennsylvania-based biotech Protez Pharmaceuticals in a deal worth up to $400 million, giving it rights to an antibiotic which could be used to fight superbugs such as MRSA. The deal underscores big pharmaceutical companies' growing appetite for promising assets developed by small biotech companies.

"(The) acquisition of Protez Pharmaceuticals provides rights to PZ-601 and further strengthens (our) specialty medicines development portfolio in hospital infections," Novartis said in a statement. PZ-601 is a novel, broad-spectrum antibiotic given by injection, which is currently in mid-stage Phase II development against potentially deadly drug-resistant infections, including MRSA and ESBL. Novartis hopes to submit it for regulatory approval in 2012. The Swiss group will pay $100 million immediately for the business, with a potential for up to $300 million of additional payments depending on the future success of PZ-601.

The emergence of hospital superbugs such as methicillin resistant Staphylococcus aureus (MRSA) and extended-spectrum beta-lactamase enterobacteriaceae (ESBL), which are resistant to existing medicines, has increased the need for alternative treatments and re-focused drugmakers' attention on antibiotics. Most so-called "superbug" infections are acquired while patients are in the hospital. According to the CDC, 2 million people in the US develop hospital-acquired infections each year, while in Europe there are an estimated 3 million infections.

PZ-601 belongs to class of antibiotics known as carbapenems. A 100-patient, Phase II study was started by Protez in May 2008 in the United States and Novartis said it would now initiate additional clinical trials. (Source: Katie Reid, Reuters, 4 June 2008)

Investors Support Biogen Idec vs. Icahn

Biogen Idec Inc. won some breathing room after a showdown at its annual meeting in June at which the biotech's shareholders defeated a slate of directors proposed by billionaire investor Carl Icahn. Neither side released voting totals, but both said Icahn's three candidates failed to win the support of enough shareholders, who instead backed a group of directors nominated by Biogen management. Alexander Denner, one of Icahn's nominees, declined to discuss what steps his side might now take. Icahn has reported owning more than 4 percent of the company and recently pushed for it to be sold to a larger drug maker.

The results should provide Biogen Idec more stability to focus on drug development and reduce the pressure to find a partner, said Leerink Swann & Co. biotech analyst Bill Tanner. "This allows them to focus on moving the ball down the field," Tanner said. "You can't be for sale all the time, or employees will say there's too much disruption."

Company executives didn't directly criticize Icahn or his efforts to gain supporters on the board. In a statement disclosing the voting outcome, chairman Bruce Ross said, "We look forward to turning our undivided attention to delivering strong performance and growing our business for stockholders."

Speaking with reporters after the meeting, Denner said his side realized it wouldn't likely prevail after proxy review firms such as RiskMetrics Group had recommended against its slate of candidates this month. Denner said Icahn's group believed it still deserves at least a seat on the board given its stake in the company. Biogen Idec has 4,000 employees including 1,700 in Massachusetts. (Source: Ross Kerber, The Boston Globe, 20 June 2008)

Worldwide Sales of Biotech Drugs Rise to $75b in '07; Growth Slowed by Generics

Global sales of biotech drugs grew 12.5 percent in 2007 to more than $75 billion, almost double the 6.4 percent growth in the overall pharmaceutical market, according to an IMS Health report. However, biotech sales slowed from the 18.2 percent growth seen in 2006, a result of competition from generic biotech drugs, particularly outside the US; greater competition in some therapeutic areas, leading to weaker sales growth; insurers raising the bar in covering treatments; and growing safety concerns for some therapies, the report said.

The healthcare research firm expects biotech sales growth to moderate through 2012, though it expects companies' research and development pipelines to remain strong. Biotech drugs currently account for 25 percent of those pipelines. The report also noted only three new biotech drugs launched in 2007, a significant decline from the prior year. However, six biotech drugs with a market potential of $1 billion are expected to launch by the end of 2009. In 2007, 22 biotech drugs had sales of at least $1 billion, compared with six in 2002.

One biotech area that experienced a decline in sales last year - 9 percent - was anemia treatments known as erythopoesis-stimulating agents. The drugs, including Amgen's Epogen and Aranesp, and Johnson & Johnson's Procrit, have received FDA scrutiny, resulting in strengthened warning labels on the drugs recommending use only in those with incurable cancers.

The US remained biotech drugs' largest market in 2007 commanding a 56 percent share of total sales, while the five major European markets had 24 percent and Japan 5 percent. (Source: Associated Press, 18 June 2008)

Wyeth Shares Rise on Promising Study of Alzheimer's Drug

Drug maker Wyeth said an investigational product for treating Alzheimer's showed promise in an intermediate clinical study. The product, called bapineuzumab, is one of 23 different avenues Wyeth is exploring under its so-called "war on

Alzheimer's." The company said that bapineuzumab improved cognitive functioning in a subset of patients, those who did not carry a genetic variation called ApoE4. Non-carriers make up 40 to 70 percent of Alzheimer's patients.

The results were important because on a test of cognitive functioning in Alzheimer's patients, the mean score decline over 18 months is 6.5 points. In the 18-month study of bapineuzumab, the patients negative for ApoE4 declined 2 to 2.5 points, or 4 points better, according to Ian Sanderson, senior research analyst for Cowen & Co. "Anything north of a 2 point spread would be considered clinically significant," Sanderson said.

Wyeth said MRI results of those same patients showed less loss of brain volume among treated patients compared with those given a placebo. Wyeth chief executive Bernard J. Poussot said the company was "encouraged" by the findings. The results were deemed positive despite the fact that the study of 240 patients did not meet its primary endpoints. That was because the drug did not appear to have the same effect on patients carrying the ApoE4 gene. (Source: Stephanie Saul, New York Times News Service, 18 June 2008)

Alnylam's RNAi Drugs to be Licensed by Takeda

Japanese drug maker Takeda Pharmaceutical Co. Ltd. has expanded its efforts to become a huge player in the Cambridge life sciences space, with a new deal worth up to $1 billion to license RNAi drugs from Alnylam Pharmaceuticals Inc. The deal comes a month and a half after Takeda announced that it would acquire Cambridge biotech firm Millennium Pharmaceuticals Inc. in a landmark deal valued at $8.8 billion, showing that Takeda is rapidly hitching its future in the oncology market to science and products made in Massachusetts.

The Alnylam deal gives Takeda the right to be the first company to negotiate development and commercialization agreements on Alnylam's RNAi drugs for the Asian market (except for ALN-RSV01, an experimental treatment for respiratory syncytial virus) for five years. It also enables Alnylam the option to be the US commercial partner of Takeda-developed RNAi treatments.

RNAi drugs are designed to inhibit the expression of certain genes linked to diseases. Alnylam's leadership in the field has brought it other large deals with big drug companies such as Swiss pharma giant Roche Holding AG, which has research and development operations in Cambridge.

Takeda has agreed to pay Alnylam $100 million in initial fees and $50 million soon in technology-transfer and licensing payments to access Alnylam RNAi technology for the fields of oncology and metabolic diseases; additional R&D and milestone sums could make the deal worth up to $1 billion to Alnylam. The firms also said that Takeda has the option to expand the deal into additional therapeutic areas for $50 million per field.

With its nearly $9 billion sale closed, Millennium is now a wholly owned subsidiary of Takeda and will continue operations in Cambridge as a standalone business unit, keeping the Millennium name. Takeda also decided to keep Millennium's executive team in place: Millennium CEO Deborah Dunsire is president of the subsidiary and reports directly to Takeda President Yasuchika Hasegawa.

Massachusetts isn't the only region of the US on Takeda's radar, however. In April, South San Francisco-based Cell Genesys Inc. agreed to sell worldwide commercial rights for its experimental prostate cancer treatment to Takeda in a deal that could be worth up to $270 million. Takeda agreed to make an initial $50 million payment followed by future payments if the drug is approved for sale and achieves revenue goals. (Source: Mass High Tech, 30 May 2008)

Investor Interest in Life Sciences Still Healthy as OmniGuide Lands Financing

Despite recent turmoil in the credit and stock markets, investors continue to pour money into local life sciences start-ups. In the latest example, OmniGuide Inc., a Cambridge company that has developed a laser scalpel for minimally invasive surgery, plans to say that it raised $25 million in its fifth round of venture financing, led by Psilos Group, a New York healthcare investment firm. OmniGuide, which has raised nearly $75 million since it was founded in 2000, is based on technology pioneered at MIT with government funding.

At MIT, OmniGuide chief executive and cofounder Yoel Fink and other scientists developed a thin, flexible, hollow fiber, lined with a special mirror-like coating, that can carry a carbon-dioxide laser beam. The laser, in turn, can be used to carve away tumors or make incisions, without disrupting the surrounding or underlying tissue. And because it is carried by a flexible fiber, Fink said, doctors can thread it through a nose, mouth, or other opening (such as a tiny incision) without major surgery.

Unlike many small companies that raise venture capital, OmniGuide already has a product on the market. The FDA cleared its fibers for sale in 2005. OmniGuide sells the fibers, which are designed to be used only once, for $600 to $1,100 apiece, in conjunction with a $30,000 laser system made by a partner. But sales are still modest. OmniGuide, which has 80 employees, recorded $2 million in revenue last year and is on track to take in more than $7 million this year.

Fink is betting sales will grow as more hospitals and doctors embrace the system. The system is currently used mainly by ear, nose, and throat specialists, but Fink said it could in coming years be used by neurosurgeons, spinal surgeons, gynecologists, gastroenterologists, and other surgeons. Eventually, Fink said, the fiber could also be used to carry laser beams in other applications, such as telecommunications.

OmniGuide is at least the fifth Massachusetts life sciences company to raise $25 million or more in venture funding in the past month. Concert Pharmaceuticals of Lexington raised $37 million, Constellation Pharmaceuticals of Cambridge brought in $32 million, Bedford-based Resolvyx Pharmaceuticals garnered $25 million, and Stromedix, another Cambridge biotech, hauled in $25 million. "It's a good time [to raise money] if you've got a good idea and good people," said Stephen Knight, managing partner of Fidelity Biosciences in Cambridge, a venture arm of Fidelity Investments. "The pharmaceuticals industry is in need of great products and technologies. And the biotech industry has proven to be a great source of innovation. In addition, major pharmaceutical companies recently snapped up two Cambridge biotechs at significant premiums: Takeda bought Millennium for $8.8 billion, and GlaxoSmithKline bought Sirtris for $720 million. (Source: Todd Wallack, The Boston Globe, 15 May 2008)

Wyeth Drug Hits New FDA Snag

Wyeth was dealt and additional setback with bazedoxifne, a proposed treatment for postmenopausal osteoporosis, as it received another "approvable" letter from the FDA. An approvable letter indicates that more information is needed before a drug can be approved. This is the third such letter that Wyeth has received for the drug, which is branded as Viviant. The Madison, NJ drug maker said that in the letter the FDA asked for more information about the incidence of stroke as well as for more source documents. The company said it has been working with the FDA to answer the agency's questions and expects to file a complete response by year end. (Source: The Wall Street Journal, 24-25 May 2008)

Pfizer and AVANT Immunotherapeutics Ink Licensing & Development Agreement For Brain Cancer Vaccine

Drug giant Pfizer and the Celldex Therapeutics unit of Cambridge-based AVANT Immunotherapeutics have entered into an agreement under which Pfizer will be granted an exclusive worldwide license to the CDX-110 cancer vaccine candidate currently in Phase 2 development for the treatment of a form of brain cancer called glioblastoma multiforme or GBM. AVANT and Celldex combined during the first quarter of 2008.

CDX-110, which has been granted both Fast Track and Orphan Drug designations by the FDA, is an investigational immunotherapy that targets the tumor-specific molecule EGFRvIII, a functional variant of the epidermal growth factor receptor (EGFR) protein that has been well validated as a target for cancer therapy in certain tumor types. The agreement also gives Pfizer exclusive rights to the use of EGFRvIII vaccines in potential indications other than GBM. "We are excited about the potential for CDX-110 and intend to partner with AVANT and academic physician-scientists to investigate this novel vaccine candidate with the hope of providing patients and doctors with a new treatment option for this devastating disease," said Dr. Briggs Morrison, Senior Vice President for Clinical Development at Pfizer.

Under the licensing and development agreement, Pfizer will make an upfront payment to AVANT of $40 million and will make a $10 million equity investment in AVANT. Pfizer will fund all development costs for these programs. AVANT is also eligible to receive milestone payments exceeding $390 million for the successful development and commercialization of CDX-110 and additional EGFRvIII vaccine products, as well as double-digit royalties on any product sales. The agreement is subject to approval under the Hart-Scott-Rodino Antitrust Improvements Act of 1976 (as amended) and is expected to close in the second quarter of 2008.

CDX-110 is designed to induce or enhance the body's immune responses against EGFRvIII, resulting in destruction of tumor cells that express the variant receptor. Early efficacy and safety data from single arm Phase 2 clinical trials of CDX-110 in combination with the current standard treatment for patients with GBM are very encouraging. Progression-free survival and overall survival data from these trials compare very favorably with historical control data. A randomized Phase 2 trial is ongoing.

GBM is the most common and aggressive form of primary brain tumor, with very poor prognosis. There are an estimated

10,000 new cases of GBM annually in the United States, which predominantly affects adults aged 45 to 70. The current standard treatment for patients with GBM includes surgical resection, radiotherapy with concurrent temozolomide and then adjuvant temozolomide chemotherapy.

In addition to CDX-110, AVANT has several other product candidates in its development pipeline including: CDX-1307, which is in two Phase 1 clinical trials for patients with advanced pancreatic, bladder, breast and colon cancer; TP10, a complement inhibitor, in development for transplantation and other indications; and three candidates based on its oral, rapidly-protecting, single-dose and temperature-stable vaccine technology, including combination vaccines for travelers, the military and global health needs.

AVANT has three commercialized products, including Rotarix (partnered with GSK) for the prevention of rotavirus infection and two human food safety vaccines for reducing salmonella infection in chickens and eggs. (Source: Celldex Therapeutics Website, 16 April, 2008)

New Members

Mr. Benjamin Greenbowe, Vertex Pharmaceuticals

Mr. Roy Robblee, North Shore Mechanical Contractors Inc.

Mrs. Annette E. Sylvester, Shire HGT

Mr. Dennis Lucey, PMA Consultants

Mr. Joseph Bellusci, MannKind Corporation

Mr. Rich Mccampbell, Jr., Clark, Richardson, Biskup

Mr. Mark Muscato, Biopure Corporation

Mr. Mauricio A. Barraza, Acceleron Pharma

Mr. David J. Caldwell, ITT Corp. - Jabsco

Nicholas R. Dion, Shire Pharmaceuticals, HGT

Mr. Brian J. Gilan, Biopure Corporation

Mr. Gary Reichert, Boston Scientific

Mr. Arturo R. Blanquera, Shire HGT

Drewe A. Brown, Siemens Water Technologies Corp

Mr. Daniel Paquette, CFM, Millennium Pharmaceuticals

Ms. Risa Glass, Wyeth Biopharma

Mr. Zeke Johnston, Genzyme

Mr. Shaun LeBlanc, Wyeth Biopharma

Zebulon J. Jones, Lonza Inc.

Steve Nole, Schneider Electric

Eduardo Handoko, Vertex Pharmaceuticals

Jorge M. Quinones, ImmunoGen, Inc.

Ms. Filomena M. Rego, Bristol-Myers Squibb

Mr. Andrew G. Torchia, AGT Consulting

Back

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

Powered By NMDeluxe with enhancements by Ashdown Technologies, Inc.