

## **High-containment, Clinical-trial Production Facility at St Jude Children's Research Hospital**

*Biologics Produced in GMP Facility Lead to New Vaccines*

In April of this year the U.S. Food and Drug Administration (FDA) announced the first approval in the United States of a vaccine for humans against the H5N1 influenza virus, commonly known as avian or bird flu. The announcement also marked a turning point for the new Good Manufacturing Practices (GMP) research facility at St. Jude Children's Research Hospital in Memphis, Tenn.

“This is the first major new vaccine that can be traced directly back to specific research that began from a seed bank within our GMP facility,” says John Coleman, vice president of the St. Jude Therapeutics Production and Quality department. “When the GMP facility opened in 2003, the facility's studies included avian flu research conducted by Robert Webster, Ph.D., a member of the St. Jude Infectious Diseases department and an internationally-renowned expert on bird flu viruses.”

Coleman adds that St. Jude was uniquely positioned to conduct these studies because it houses Webster's large collection of bird flu viruses gathered over several decades. St. Jude is also one of six Centers of Excellence for Influenza Research and Surveillance funded by the National Institute of Allergy and Infectious Diseases, which is part of the National Institutes of Health.

### **A Facility Overview**

The GMP center is a 62,000-sf, three-story biocontainment facility in which up to 12 clinical-trial production projects can be run simultaneously for applications ranging from avian flu, HIV, gene therapy, and monoclonal antibodies. The facility is equipped to produce highly specialized medicines and vaccines under government-approved GMP procedures and standards of operation established by the FDA.

“The GMP facility was built to support the hospital's goal of taking research directly from discovery in the laboratory and quickly moving it into clinical trials,” says Coleman. “When we opened, we were the only pediatric cancer research center in the nation with an on-site facility for producing vaccines, drugs, proteins, gene-based molecules, and other biological products.”

He adds that the GMP facility is devoted specifically to small scale biologics production for use in development of cellular therapies, vaccines, immunotherapies, gene vectors, and proteins. The facility's largest scale projects are conducted in a 100-liter bioreactor.

“Our focus is on very small lots such as small-scale flask bioreactors and single patient treatments for use in phase one and phase two clinical trials,” says Coleman. “Once we prove efficacy or at least proof of principal, our research results can be taken by pharmaceutical companies to conduct more large scale research before it becomes available for widespread use.”

In total the St. Jude facility houses 12 GMP production suites, two of which are BSL-3 laboratories that can accommodate work with microorganisms that require strict containment procedures. The first and second floors of the facility contain a combination of 27,000 sf of production space and 19,000 sf of administrative space that includes offices, document storage areas, two conference rooms, a training room, and space for materials handling and waste management. The third floor is devoted entirely to mechanical/electric systems, including all of the air handlers, pure steam generators, clean steam generators, and VAV control boxes.

### **Preventing Cross-Contamination**

“Due to cross-contamination concerns and safety issues involved in dealing with Select Agents, hospital security transferred control of the badge access to me for the GMP facility,” says Coleman. “So on a campus of more than 3,200 people, only about 50 people have access to this facility.”

He adds that cross-contamination is also of high concern at St. Jude because of the variety of different organisms and biologics used within the site.

“All of the cell lines and the viruses used for either viral gene therapy production or bacteria are initially taken into our cell banking area on the first floor,” says Coleman. “The cells are then expanded so that we can verify their identity and check for purity to make sure no other agents are contaminating the cell.”

Coleman points to the facility’s depyrogenation oven as another example of specialized equipment used within the GMP facility to prevent cross-contamination.

“Our aseptic fill room has a depyrogenation oven, which is basically an autoclave without steam,” says Coleman. “It uses dry heat at extremely high temperatures to burn off anything that might be on glassware before cells are put into small vials as the final production step before release.”

Each of the GMP production rooms is protected by airlock access and include two fixed biosafety hoods. Since there is no other fixed equipment in the production rooms, equipment is moved in and out based upon the requirements of that particular production. The rooms are all cleaned, inspected by Quality Assurance (QA), and environmentally monitored before new production starts.

“To reduce the number of penetrations in our production room walls, we worked with our architect to develop a unique utility panel for our mechanical and electrical systems,” says Coleman. “The panel was specifically designed so that there was only one large hole in the wall that needed to be sealed within the production rooms.”

## Controlling the Flow

Coleman points to establishing a proper flow of materials and people as another method of preventing cross-contamination and contamination of products within biocontainment facilities.

“When raw materials come into the GMP’s receiving dock, our QA unit inspects the materials based on FDA regulations,” says Coleman. “When a production team wants materials, they are required to present a written request to the QA unit who then provides the materials needed for that production run.”

He adds that the GMP uses unidirectional process flows for materials, equipment, and people so that all production rooms have specific entrances and exits that lead to related gowning areas.

“The first and second floors each have central hallways that serve as a clean corridor, with airlocks leading into production rooms located on either side of the hallway,” says Coleman.

Level-one gowning requires dedicated scrubs, shoes, and shoe covers. It gives workers access to such things as autoclaves for maintenance purposes, quality assurance, and final product storage areas.

Level-two gowning is required to enter into the GMP’s actual production areas. This requires sterile outer garments, face masks, hair nets, gloves, and respirators when working with Select Agents in the BSL-3 areas.

Most of the waste from the GMP facility is chemically decontaminated in place before it leaves each production room. Additional waste is decontaminated in an autoclave near the loading dock or incinerated when necessary.

Coleman explains that containment within the GMP facility is also achieved through air pressurization and interlock doors that prevent more than one door from opening simultaneously.

“Our production rooms, which are ISO Class 7, use one-pass air and all rooms receive more than 50 air exchanges per hour,” says Coleman. “We do not repeat circulation of any air into our production rooms in order to prevent cross-contamination and we use different pressures to control air flow.”

“After operating for several years, the only facility regret I can pinpoint is that it would be nice to have more space for development activities,” he concludes. “If we were to build a similar facility in the future, my recommendation would be to devote more lab space specifically to developmental research activities and quality control testing.”

**Biography:** **John Coleman** is vice president of the Therapeutics Production and Quality department at St. Jude Children's Research Hospital in Memphis, Tenn. He is also president of Children's GMP Limited Liability Company. In both capacities, Coleman is involved in producing biological products for clinical trials. Prior to his association with St. Jude Children's Research Hospital, Coleman served as director of the Molecular and Cellular Therapeutics facility at the University of Minnesota where he built and managed a cGMP production facility for the University. For 20 years prior to that, he worked for Dow Chemical managing biotechnology research programs and doing process development for therapeutic proteins and scalable cGMP manufacturing processes.

This article is based on Coleman's presentation at the Tradeline *2007 International Conference on Biocontainment Facilities* held in March.

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The GMP at St. Jude Children's Research Hospital in Memphis, Tenn., can run up to 12 clinical-trial production projects simultaneously. *(Photo courtesy of St. Jude Children's Research Hospital.)*



Card key access is required to enter the cell banking area, which includes a storage tank for frozen cells that are quarantined in liquid nitrogen. *(Photo courtesy of St. Jude Children's Research Hospital.)*



This depyrogenation oven, which is required as part of GMP regulations, uses dry heat at extremely high temperatures to burn off contaminants and proteins from glassware and glass vials. *(Photo courtesy of St. Jude Children's Research Hospital.)*