PDA Parenteral Drug Association
Southeast Chapter

The PDA Southeast Connection

Connecting People, Science and Regulation

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Early Trials Manufacturing and Product Consistency in the Biotech Industry

Presented by Tatyana Touzova
Senior Director of Quality Assurance
Biolex, Inc.

Summary by Kathleen Merold, GlaxoSmithKline

Tatyana Touzova, Senior Director of Quality Assurance at Biolex Therapeutics Inc. discussed her experiences bringing a product through numerous stages of drug development in the biotechnology industry. The product is derived from a plant. The Novel Plant Based Expression system allows for simple nutritional requirements, a contained/controlled environment, robust growth conditions, clonal propagation, and low capital requirements. There are no requirements for animal sourced material.

The different activities for each phase of development were discussed. A quality system was implemented early when preclinical studies were completed. For example, developmental standard operating procedures, batch records, and test methods were created. It was important to design and construct the manufacturing facility so that utilities, equipment, and facility met specific requirements during the Phase 1 and Phase 2a Clinical GMP manufacturing. Environmental monitoring was implemented in classified and non-classified/controlled areas and action levels were established based on ISO standard. A Validation Master Plan was developed as well as performance qualifications of the Purified water system and utilities. Cleaning verification

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Join PDA Southeast Chapter
Thursday, December 4th from 5:30 - 7:30pm
for our
2nd annual Winter Social in
Celebration of the Season and our University Student "Stars".

As you mingle with fellow PDA Members and industry guests,
you can gaze at the works of art at Gallery C, while
enjoying hors d'oeuvres and a complimentary beverage.

Student Scholarship Award Winners will be announced

Introduce your peers to PDA Southeast Chapter
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This event is complimentary, we ask that you
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continued...

Early Trials Manufacturing and Product Consistency in the Biotech Industry

for resins and equipment was implemented. Numerous other aspects of drug development in Phase 1 and Phase 2a required development. This included manufacturing, concerns about the quality systems, and interaction with Quality Control.

Clinical Manufacturing in Phase 2b required some adjustment for quality systems, manufacturing, and quality control. Some examples of changes made in Phase 2b are: the implementation of the in-process controls based on phase 2a historical data, monitoring of process performances, establish column life cycle, validation of resin cleaning, and establish specifications for the buffer.

A cross functional team approach will be used for Phase 3 preparedness. This team includes the following areas: Quality Systems, Material Control, Quality Control, Training, Engineering, Manufacturing/Manufacturing Science, Human Resources, Project Management, and Finance. A Phase 3 Preparedness Steering Committee was initiated to assure team activities are aligned with company's goals, provide senior management support for team, and allocate resources to meet team objectives. Activities for each functional team were presented.

It was interesting to hear how a product derived from a plant is being brought through the drug development process. Numerous challenges were met, such as developing environmental conditions to grow the plant within the facility. There are challenges ahead, such as the requirement for more facility space and employees to get this product to market.

Members In the News

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Mitigating Raw Material Risk For Supply Chain Management

Presented by John Hollenbach, Doe & Ingalls of NC

Summary By: Anthony Pavell MKCS Inc.

There are many influences driving the focus on risk mitigation for raw material supply including; globalization of the supply chain, FDA interest in risk mitigation, and lean manufacturing practices being implemented in the pharmaceutical industry. In order for the industry to mitigate risk effectively, you need to understand the total supply chain risk from the source material through global distribution of the raw material with consideration of systematic risk versus specific risks.

There are a few key systematic risks to the chemical market today. The transparency of documentation to the original source material is a major challenge. Some raw materials used today do not have compendia established and there is limited oversight from foreign and domestic drug regulators over global raw material suppliers. Additionally there are specific risks factors to pharmaceutical grade raw material supply. The chemical manufacturers are not focused on the pharmaceutical industry, materials may be sole sourced and the transparency into the supply chain is limited which all effect GMP production and supply. A case study was presented related to Isopropanol. There are apparently only 4 producers of USP and ACS grade IPA in the world with three locations in the US. The pharmaceutical industry consumes approximately 4 percent of the IPA produced representing a very small market share. A shift in the production method or focus would significantly impact GMP usage of IPA.

The identified risks can be placed into categories of: Production, Environmental, Counterfeit/Contamination, Production Changes, and Geopolitical (tariffs).These risk categories must be considered in a planned risk assessment. When performing a risk assessment it is most important to decide on the scope of assessment (all materials or critical only) and involve the appropriate personnel including purchasing, planning, development, and quality. The risk assessment process will map each material being assessed based on a determined criticality of material to the production process and the ability to detect the risk. This map will be used to prioritize materials for the development of material specific risk mitigation action plans.

The Risk Mitigation Action Plan will include a plan to address when materials arrive that are most significantly out of range when compared to specification. A list of immediate actions to take to mitigate production risk due to the out of specification result should include an assessment of current inventory and the ability to use an alternate supplier. For process critical materials consideration should be given to long term action such as capacity agreements, supplier agreements, or regular audits to maintain inventories. A cost-benefit analysis comparing the cost of the mitigation measures to the cost of failure/ceased production should be included in mitigation plan. Finally a mitigation plan should set up a program to monitor the planned measures and re-evaluate the material risks. The result of the mitigation initiatives should be an efficient and effective method to take high risk materials to a medium category or even lower if possible to limit the risk to your product and company.

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Disinfectants and Sporicides to Address Mold and Bacterial Spore Outbreaks

Presented by Jim Polarine, Steris Corp.

Summary By: Anthony Pavell MKCS Inc.

Excursions for microbial contamination occur in facilities and the causes vary. Some of the causes include setting inappropriate microbial limits, facility design flaws, barrier failures, personnel practices and cleaning/sanitization program failures. It has been the Jims' experience that many sites do not set an appropriate limit for microbial recoveries. Jim specifically stated that it is unreasonable to set a limit of zero molds for many of the sites in a facility since this is such a common organism in the environment.

When an excursion is identified it is important to start troubleshooting immediately and identify what has changed at the facility. One of the investigation focus point should be on the application conditions of the cleaning agent and disinfectant. Some of the question to ask are: Has there been a change in applied concentration?, was the contact time shortened?, has the temperature of the area changed (starting use in a cold room), has the diluent been changed?, has the surface being cleaned changed due to repair?, has the bioburden or soil levels increased recently? A review of the application techniques should also be performed to see if anything has changed as compared to the previous procedure. The application techniques should include applying the disinfectant to a wiper or spraying it on the surface to be disinfected. The diluted disinfectant solution should be changed, when using a bucket system, at least every 600 square feet for an ISO 5 area and changed every 1000 square feet for ISO 6, 7 and 8 areas. Some alternative application techniques to wiping/moping were discussed. The alternative techniques include foaming (animal areas primarily) vaporized hydrogen peroxide, spraying/aerosolizing, fumigation and full immersion. These techniques all have their positive and negatives that need to be considered when selecting an application method to use in facility. Whatever method is selected must have the disinfectant efficacy qualified for use at the facility following current industry guidance including USP General Chapter 1072, ISO 14698 Part 1-3 and the FDA Aseptic Processing Guide, 2004.

A case study was presented for mold reduction using various disinfectants. The study was performed using mostly *Aspergillus* spp, *Candida* spp, and *Penicillium* spp. The study documented that phenolic disinfectants were not as effective as sporocides against these mold species. The phenolic results averaged around a 3 log reduction at contact times ranging from 3 to 15 minutes while the hydrogen peroxide results averaged around a 6 log reduction at the same times and same challenge surfaces. Even a challenge using 70% IPA actually proved effective against spores, 4- 5 log reduction, at contact times as short as 30 to 120 seconds.

Hard surface test data was presented for the reduction of B. *subtilis* (ATCC 19659) on materials such as glass, stainless steel, vinyl and acrylic. The results presented showed an average of the 3 log reduction of spores after only a 5 minute exposure to H2O2/PAA. The reduction mention in USP General Chapter <1072> is that you should obtain a 2 log reduction of spores and a 3 log reduction of vegetative cells on a hard surface efficacy test.

A question was asked by the audience related to glass walls installed in modern pharmaceutical plants. Jim recommended rinsing the walls after your disinfectants contact time with either WFI or 70% IPA for residue removal. This is easily done since approximately 80 to 90% of the residue is dried surfactants from the cleaner or disinfectant.