Win-Win With University Partnerships and Your Society

American Institute of Chemical Engineers (AIChE) Cleveland Section #017

Joseph Yurko, PE; Associate Project Lead, Xellia Pharmaceuticals, USA
Past Chair, AIChE Cleveland Section #017

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Win-Win With University Partnerships and Your Society

OVERVIEW OF PARTNERSHIP APPROACH TEMPLATE (for society / company contact)

- **Engage local universities to participate in partnership**
  - Discipline of Engineering (i.e, AIChE, ASME, IEEE, ISA…etc.)
  - Contact Student Chapter Advisor at local university (CSU, CWRU…UA)
- **Propose a program of interest between company and university**
  - Lunch & Learn: Develop 40 min. presentations on 12 weekly topics
  - Internship: Develop a series of weekly input/output steps for students
- **Provide a schedule of milestones to be accomplished**
  - Lunch & Learn: Create a midterm and final open group exam
  - Internship: schedule what deliverables are due and when
- **Set the expectations for the final product to be delivered**
  - Lunch & Learn: attend and participate in presentations and exams
  - Internship: Turn over of project files after project presentation is made

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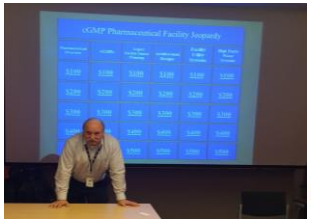
Lunch & Learn Partnership Summary (CSU)

- **Prepare 12 modules supporting skills to be presented over 12 weeks**
  - Modules should be in MS PowerPoint, about 40 minutes, text and visuals for illustration
  - Modules should have a summary screen of topics and an overall list of modules
- **Focus module content on subject matter your company needs**
  - Stay specific to your industry to maintain clarity and focus for student absorption
  - Begin with simpler or general topics initially and move to be more detailed later
- **Subject matter may be beyond students studies but not beyond abilities**
  - Subject matter should be new to student and presented as an introduction
  - Subjects should be general initially and later move to more specific details
- **Midterm and Final Exams**
  - Group/open participation (not written) should be done to reinforce concepts and have fun
  - Example: for Pharmaceuticals a “Jeopardy” style game was with three letter acronyms



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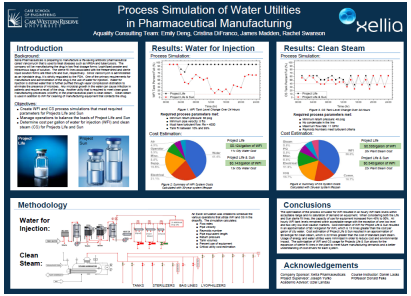
Internship Partnership Summary (CWRU)

- **Develop Project / Program for execution valued by your company**
  - Project with PFDs and Scope of Work issued to vendors for quotes
- **Make it a SMART Project / Program**
  - SMART: Specific, Measurable, Achievable, Relevant and Time Bound
- **Hold the students accountable in weekly status report meetings**
  - Provide a weekly status report template for the students inputs and outputs.
  - Have the students work in a consulting company concept with an hourly rate fee.
  - Have the students consider the agreement contract be: Fixed Price or Lump Sum.
  - Award a value (reasonable) to the students for the contract, and deduct weekly hours worked.
  - Present a Scope of Work to students for understanding of project deliverables and schedule.
  - If students decide to add changes to the Scope of Work then they need a Contract Change Form.
  - The Change Form will have the change, justification and impact of Mandays (costs) to project.
  - The straight time of the students on the project is for 4 students to work a combined 40 hour week.
  - The students need to keep track of their hourly time If they exceed a 40 hour week.
  - At the end of the project the students will see their profit/loss based on hours worked.
- **In conclusion review the project for "Lessons Learned" and review profit/loss**



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Fall Semester Lunch & Learn Series in Summary

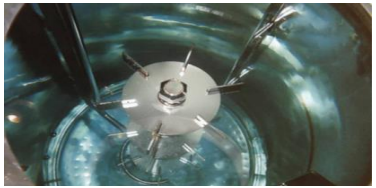
1.	Pharmaceutical Industry Profile	Thursday, September 06
2.	Current Good Manufacturing Practices	Thursday, September 06
3.	Legacy Facility Master Planning	Thursday, September 06
4.	Commissioning, Qualification, and Validation	Thursday, September 13
5.	Facility Utility Systems	Thursday, September 20
6.	QA / QC Laboratories and Related Support Spaces	Thursday, September 20
7.	High Purity Water Systems	Thursday, September 27
8.	Architectural Design & **Midterm Exam**	Thursday, October 04
9.	Sterile Manufacturing Facilities	Thursday, October 11
10.	Biotechnology Facilities	Thursday, October 18
11.	Codes and Standards	Thursday, October 18
12.	**Process Engineering**	**Thursday, October 25**
13.	Containment Technology (Isolators & RABS)	Thursday, October 25
14.	Occupational Health and Safety	Thursday, November 01
15.	Sustainability (LEEDs)	Thursday, November 08
16.	Process Automation	Thursday, November 08
17.	Packaging and Warehousing	Thursday, November 15
18.	**Final Exam**	Thursday, November 29
19.	Awards Ceremony	Thursday, December 06

Lunch & Learn Module # 12, Process Engineering in Summary

- **Process Engineering**
  - History of Pharmaceutical Industry Processing
  - Role of Process Engineering in Pharmaceutical Industry
  - Relationship of Process Engineer to other disciplines
  - Impact of cGMPs on Process Engineering
  - Typical Processing Technologies
  - Pumping of Parenterals
  - Mixing of Parenterals
  - Heat Transfer of Parenterals
  - Reaction of Parenterals
  - Filtration of Parenterals
  - Homogenization of Parenterals
  - Freeze Drying, Lyophilization of Parenterals
  - Vapor Compression Distillation producing WFI
  - Clean-In-Place (CIP) for Piping and Equipment
  - Steam-In-Place (SIP) for Piping and Equipment

12. Process Engineering, “Lunch & Learn”

- **History of Pharmaceutical Industry Processing**
  - Early manufacturing efforts extracted pharmacologically active chemicals form plants and animals. Willow leaves and bark yielded molecules similar to acetylsalicylic acid or aspirin.
  - In late 1800’s chemists began to develop methods to produce naturally occurring chemicals synthetically. Aspirin was first synthetically manufactured from coal tar.
  - In the 1900’s the trend of using chemical reactions to manufacture pharmaceuticals grew. After World War II fermentation was process of choice to produce antibiotics
  - Since 1980’s biotechnology has been used to produce more targeted molecules from genetically engineered multicellular and single cellular organisms
  - Today a combination of chemically produced small molecules attached to biologically produced large molecules is the trend
- **Role of Process Engineering in the Pharmaceutical Industry**
  - Process Engineering forms bridge between chemistry, biology, pharmacology and manufacturing operations
  - Scaling up unit operations and converting them into the sizing, specification, and selection of production equipment systems meeting cGMPs, installation time, and costs
- **Relationship of Process Engineering to Other Design Disciplines**
  - Support the manufacturing process operation and allowing it to function as intended
  - Facility design team: process, automation, mechanical, structural, electrical, and architectural
  - Also, manufacturing, validation, quality, and R&D scientists and engineers as required



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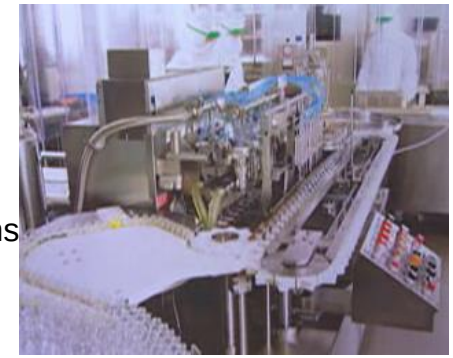
12. Process Engineering, “Lunch & Learn”

- **Impact of cGMPs on Process Engineering**
  - cGMPs require the production processes manufacture products that consistently meet quality, efficacy, and stability requirements.
  - A well documented scientific basis for process operations ensures that when they are carried out under the documented conditions, the correct drug results.
  - The process and facility are designed to prevent both trace contamination and cross contamination of drug products
  - The process engineers responsibility is to specify and design process equipment and systems that will prevent contamination and can be easily and thoroughly cleaned in the manufacturing facility to protect the product and patient
  - The International Society for Pharmaceutical Engineers (ISPE) Baseline Pharmaceutical Guides provides an excellent resource for identifying and addressing cGMP issues.
- **Typical Processing Technologies**
  - Pharmaceuticals are chemicals (API) with health effects that interact with living animals or humans
  - Production of pharmaceuticals (API) depends on chemical synthesis, extraction from natural material, biological processing, or a combination of these processes
  - After the pharmaceutical chemicals (API) are produced they must be formulated for human use
  - For injectables the API must be mixed in proper proportions with excipients (Bulking Agents, Buffering Agents, Tonicity Modifier, and Collapse Temperature Modifier) per the formulation based on the NDA Phase III Clinical Trials



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12. Process Engineering, “Lunch & Learn”

- **Pharmaceutical Processes**
- **Injectables, Finished Dosage Form (FDF)**
  - Must be sterile since they directly enter the body bypassing the protection offered by the digestive system
  - Process steps for injectables are relatively simple, those steps that ensure the product is sterile and stable are more complicated
  - The process starts with dissolving the API into Water For Injection (WFI)
  - After the formulation of the product it is filtered through a 0.2 micron filter to ensure sterility before filling a vial
  - If the API is not heat sensitive, then the filled and stoppered vials are terminally sterilized with steam
  - If the API is heat sensitive, then the aseptically filled and un-stoppered vials are freeze dried in Lyophilizers
  - Vials and all items that come in contact with the sterile product must also be sterile
- **Processing of Active Pharmaceutical Ingredients (APIs)**
  - APIs are produced by chemical synthesis biological processing or a combination
  - Extraction of natural materials from either plants or animals can be done by either process
  - API produced by chemical synthesis is done by a series of chemical reactions
  - Each chemical reaction is accompanied by a number of unit operations

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12. Process Engineering, “Lunch & Learn”

- **Pharmaceutical Processes**
- **Processing of Active Pharmaceutical Ingredients (APIs)**
  - Primary chemical synthesis unit operations are:
    - Reaction, Heat Transfer, extraction, distillation, evaporation, crystallization, filtration, drying and size reduction
  - Most chemically produced APIs are completed in the liquid phase of organic solvents
  - They are then solidified, separated from the solvent and other impurities by filtration
  - Finally they are dried under vacuum to remove the last traces of solvent
  - The dried API is then milled to reduce the particle size range for formulation into final dosage form
  - Pharmaceutical facilities that produce API require multi product, flexible equipment trains
- **Reactions**
  - Most reactions are liquid phase batch reactions inside a pressure vessel with an agitator and an external heating/cooling jacket under insulation
  - The final API frequently requires from 3 to 10 separate reaction steps based on complexity
  - Each of the reaction steps usually requires separation and some purification
  - The earlier reaction steps usually require a larger reactor and greater volumes of materials
  - The first reactor may be four to five times larger than the final reaction volumes
  - Typical production scale reactor volumes range from 500 to 5,000 gallons
  - Typical research scale reactor volumes range from 5 to 500 gallons

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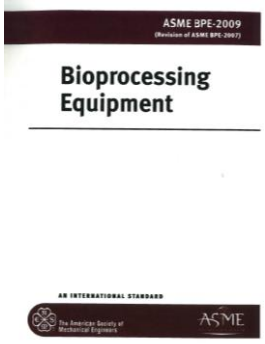
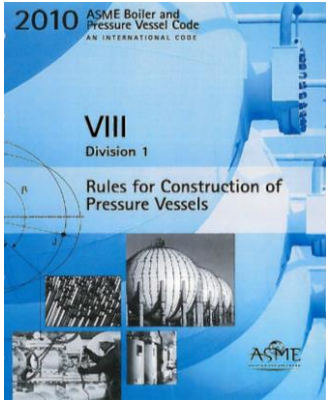
12. Process Engineering, “Lunch & Learn”

- **Reactions**
  - API production process reaction chemicals are frequently highly corrosive
  - Most common materials of construction are glass lined steel and Hastelloy C which are able to withstand high temperatures and resist corrosion
  - Associated equipment , piping, and product contact instruments must be similar materials
  - Piping materials include Teflon-lined steel, Hastelloy C, glass-lined steel, and armored glass
  - Reaction pressures are generally below 150 psig, except for some gas-liquid phase reactions which can require up to 6,000 psig
  - Reaction vessels must also be able of holding a full vacuum. This permits operations that occur below atmospheric pressure to limit the temperature exposure of the reaction product
  - Processing temperatures normally range from -20°C to +250°C, with some reactions occurring as low as -70°C





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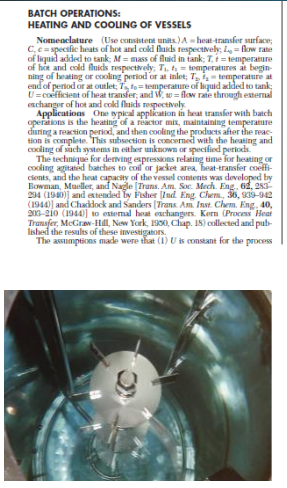
12. Process Engineering, “Lunch & Learn”

- **Reactors (Parenteral)**
  - Reactors are a batch operation
    - Mass addition of WFI, API, and Excipients (Buffer Agents, Bulking Agents, and Lyophilizatoin Thickeners) per Batch Record Formulation
    - Reactor will have legs on load cells to detect 0.01 kg of mass as formulation proceeds
    - All piping connections to Reactor will need flex hose spool pieces to prevent mass measurement dampening error
  - Reactors are agitated or mixed
    - VFD Agitation shaft and impeller are installed at an angle off center of vessel to prevent any vortexing of mixture and stratification of layers in batch
    - No baffeling is required improving cleaning of reactor by preventing baffle shadows
    - Only mixing of WFI, API, and Excipients occurs in Reactor, no chemical changes
  - Reactors are jacketed with insulation and stainless steel coverage
    - Reactor has dimpled jacket with RTD/ thermowell to control batch temperature
    - Reactor jacket has cascade temperature control with PID loop tuning
    - Minimal temperature process variable overshoot of set point occurs
    - Initial and final heat transfer phases may be unsteady-state
    - Mid operation heat transfer phase will be steady state
  - Reactors have sparged gas with top over-lay of gas
    - For stability and media runs a Reactor will test with air sparge/blanket
    - For product runs a Reactor will operate with nitrogen/ sparge/blanket
    - Excipients may have surfactant to for anti-foaming of sparged gas


BATCH OPERATIONS:
HEATING AND COOLING OF VESSELS

Nomenclature (Use consistent units.) A = heat-transfer surface; c, c = specific heats of hot and cold fluids respectively; L_h = flow rate of liquid added to tank; M = mass of fluid in tank; T, t = temperature of hot and cold fluids respectively; T_1, t_2 = temperatures at beginning of heating or cooling period or at inlet; T_2, t_2 = temperature at end of period or at outlet; T_0, t_0 = temperature of liquid added to tank; U = coefficient of heat transfer; and W, w = flow rate through external exchanger of hot and cold fluids respectively.

Applications One typical application in heat transfer with batch operations is the heating of a reactor mix, maintaining temperature during a reaction period, and then cooling the products after the reaction is complete. This subsection is concerned with the heating and cooling of such systems in either unknown or specified periods.

The technique for deriving expressions relating time for heating or cooling agitated batches to coil or jacket area, heat-transfer coefficients, and the heat capacity of the vessel contents was developed by Bowman, Mueller, and Nagle [*Trans. Am. Soc. Mech. Eng.*, **62**, 283–294 (1940)] and extended by Fisher [*Ind. Eng. Chem.*, **30**, 939–942 (1944)] and Chaddock and Sanders [*Trans. Am. Inst. Chem. Eng.*, **40**, 203–210 (1944)] to external heat exchangers. Kern (*Process Heat Transfer*, McGraw-Hill, New York, 1950, Chap. 18) collected and published the results of these investigators.

The assumptions made were that (1) U is constant for the process

nd over the entire surface, (2) liquid flow rates are constant, (3) specific heats are constant for the process, (4) the heating or cooling medium has a constant inlet temperature, (5) agitation produces a uniform batch fluid temperature, (6) no partial phase changes occur, and (7) heat losses are negligible. The developed equations are as follows. Many of the assumptions do not apply to a system being designed, now equations should be developed or appropriate corrections made. Heat exchangers are countercflow except for the 1-2 exchangers, which are one-shell-pass, two-tube-pass, parallel-flow countercflow.

Coil-to-Tank or Jacketed Vessel: Isothermal Heating Medium

$$\ln\frac{T_1-t_1}{T_1-t_2}=\frac{UAθ}{Mc} \tag{11-32a}$$

Cooling-in-Tank or Jacketed Vessel: Isothermal Cooling Medium

$$\ln\frac{T_1-t_1}{T_2-t_2}=\frac{UAθ}{MC} \tag{11-32a}$$

Coil-in-Tank or Jacketed Vessel: Nonisothermal Heating Medium

$$\ln\frac{T_1-t_1}{T_1-t_2}=\frac{WC}{Mc}\left(\frac{K_1-1}{K_1}\right)θ \tag{11-32b}$$

where $K_1=e^{UA/Wc}$

Coil-in-Tank: Nonisothermal Cooling Medium

$$\ln\frac{T_1-t_1}{T_2-t_1}=\frac{wc}{MC}\left(\frac{K_2-1}{K_2}\right)θ \tag{11-32c}$$

where $K_2=e^{UA/wc}$

External Heat Exchanger: Isothermal Heating Medium

$$\ln\frac{T_1-t_1}{T_1-t_2}=\frac{wc}{Mc}\left(\frac{K_3-1}{K_3}\right)θ \tag{11-32d}$$

External Exchanger: Isothermal Cooling Medium

$$\ln\frac{T_1-t_1}{T_2-t_1}=\frac{WC}{MC}\left(\frac{K_1-1}{K_1}\right)θ \tag{11-32e}$$

External Exchanger: Nonisothermal Heating Medium

$$\ln\frac{T_1-t_1}{T_1-t_2}=\left(\frac{K_4-1}{M}\right)\left(\frac{wWC}{K_4wc-WC}\right)θ \tag{11-32f}$$

where $K_4=e^{UA(Wc-wc)}$

External Exchanger: Nonisothermal Cooling Medium

$$\ln\frac{T_1-t_1}{T_2-t_1}=\left(\frac{K_4-1}{M}\right)\left(\frac{Wwc}{K_4wc-WC}\right)θ \tag{11-32g}$$

where $K_4=e^{UA(Wc-wc)}$

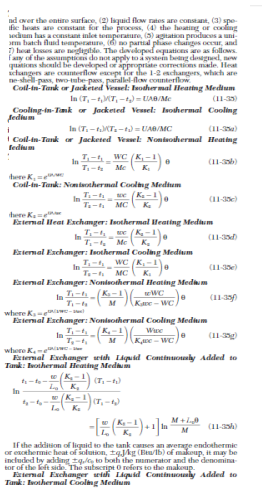
External Exchanger with Liquid Continuously Added to Tank: Isothermal Heating Medium

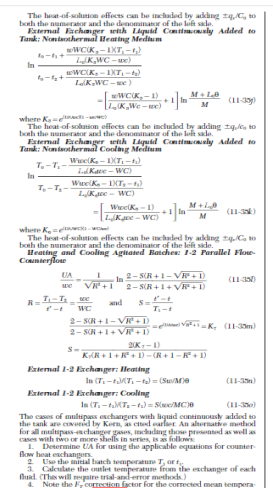
$$\ln\frac{t_1-t_0-\frac{w}{L_0}\left(\frac{K_5-1}{K_5}\right)(T_1-t_1)}{t_2-t_0-\frac{w}{L_0}\left(\frac{K_5-1}{K_5}\right)(T_1-t_2)}=\left[\frac{w}{L_0}\left(\frac{K_5-1}{K_5}\right)+1\right]\ln\frac{M+L_0θ}{M} \tag{11-32h}$$

If the addition of liquid to the tank causes an average endothermic or exothermic heat of solution, $\pm q_s$ kJ (Btu/lb) of makeup, it may be included by adding $\mp q_s/c_1$ to both the numerator and the denominator of the left side. The subscript 0 refers to the makeup.

External Exchanger with Liquid Continuously Added to Tank: Isothermal Cooling Medium

$$\ln\frac{T_0-T_1-\frac{K_1-1}{L_0K_1}(T_1-t_1)}{T_0-T_2-\frac{W}{L_0}\left(\frac{K_1-1}{K_1}\right)(T_2-t_2)}=\left[1-\frac{W}{L_0}\left(\frac{K_1-1}{K_1}\right)\right]\ln\frac{M+L_0θ}{M} \tag{11-32i}$$





The heat-of-solution effects can be included by adding $\mp q_s/C_1$ to both the numerator and the denominator of the left side.

External Exchanger with Liquid Continuously Added to Tank: Nonisothermal Heating Medium

$$\ln\frac{t_0-t_1+\frac{wWC(K_6-1)(T_1-t_1)}{L_0(K_6Wc-wc)}}{t_0-t_2+\frac{wWC(K_6-1)(T_2-t_2)}{L_0(K_6Wc-wc)}}=\left[\frac{wWC(K_6-1)}{L_0(K_6Wc-wc)}+1\right]\ln\frac{M+L_0θ}{M} \tag{11-32j}$$

where $K_6=e^{UA(wc-Wc)}$

The heat-of-solution effects can be included by adding $\mp q_s/c_0$ to both the numerator and the denominator of the left side.

External Exchanger with Liquid Continuously Added to Tank: Nonisothermal Cooling Medium

$$\ln\frac{T_0-T_1-\frac{Wwc(K_6-1)(T_1-t_1)}{L_0(K_6wc-WC)}}{T_0-T_2-\frac{Wwc(K_6-1)(T_2-t_2)}{L_0(K_6wc-WC)}}=\left[\frac{Wwc(K_6-1)}{L_0(K_6wc-WC)}+1\right]\ln\frac{M+L_0θ}{M} \tag{11-32k}$$

where $K_6=e^{UA(wc-Wc)}$

The heat-of-solution effects can be included by adding $\mp q_s/c_0$ to both the numerator and the denominator of the left side.

Heating and Cooling Agitated Batches: 1-2 Parallel Flow-Counterflow

$$\frac{UA}{wc}=\frac{1}{\sqrt{R^2+1}}\ln\frac{2-S(R+1-\sqrt{R^2+1})}{2-S(R+1+\sqrt{R^2+1})} \tag{11-33f}$$

$$R=\frac{T_1-T_2}{t'-t}=\frac{wc}{WC}\quad\text{and}\quad S=\frac{t'-t}{T_1-t}$$

$$\frac{2-S(R+1-\sqrt{R^2+1})}{2-S(R+1+\sqrt{R^2+1})}=e^{UA(wc)\sqrt{R^2+1}}=K_7 \tag{11-33m}$$

$$S=\frac{2(K_7-1)}{K_7(R+1+R^2+1)-(R+1-R^2+1)}$$

External 1-2 Exchanger: Heating

$$\ln(T_1-t_2)/(T_2-t_2)=(Su/M)θ \tag{11-33n}$$

External 1-2 Exchanger: Cooling

$$\ln(T_1-t_2)/(T_2-t_2)=S(wc/MC)θ \tag{11-33o}$$

The cases of multipass exchangers with liquid continuously added to the tank are covered by Kern, as cited earlier. An alternative method for all multipass-exchanger cases, including those presented as well as cases with two or more shells in series, is as follows:

1. Determine UA for using the applicable equations for counterflow heat exchangers.
2. Use the initial batch temperature T_1 or t_1.
3. Calculate the outlet temperatures from the exchanger of each fluid. (This will require trial-and-error methods.)
4. Note the F_T correction factor for the corrected mean temperature difference. (See Fig. 11-4.)
5. Repeat steps 2, 3, and 4 by using the final batch temperatures T_2 and t_2.
6. Use the average of the two values for F_T then increase the required multipass UA as follows:

$$UA(\text{multipass})=UA(\text{counterflow})/F_T$$

In general, values of F_T below 0.8 are uneconomical and should be avoided. F_T can be raised by increasing the flow rate of either or both

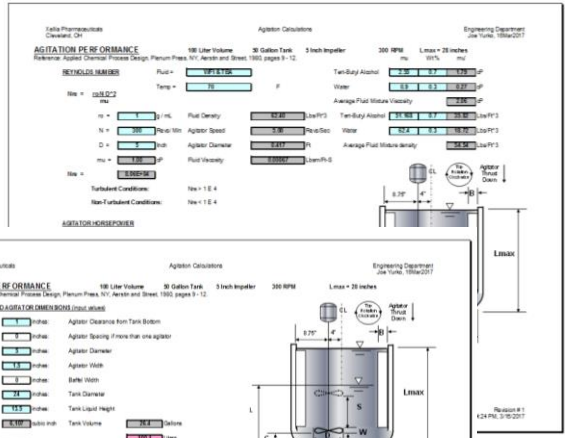
12. Process Engineering, “Lunch & Learn”

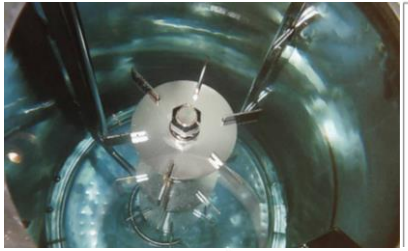
- **Mixing or Agitation (Parenterals)**
  - Newtonian Liquids (mostly WFI in compounding vessels)
    - Reynolds Number generated for system
    - Power Number generated for system
    - Agitator horsepower generated for system
    - Mixing time to achieve 95% homogeneity
  - Impeller is off-center and at angle, no baffles needed

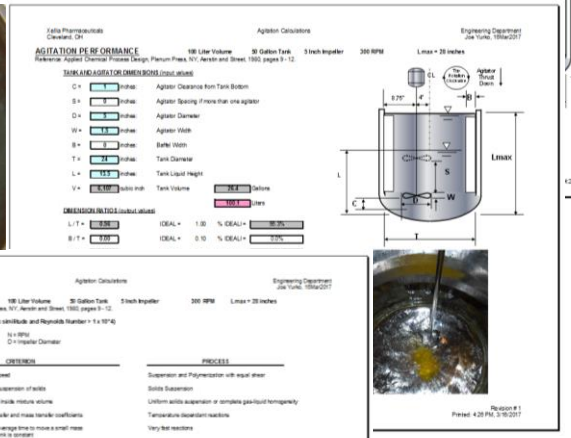
    Improved CIP & SIP operations with no shadows

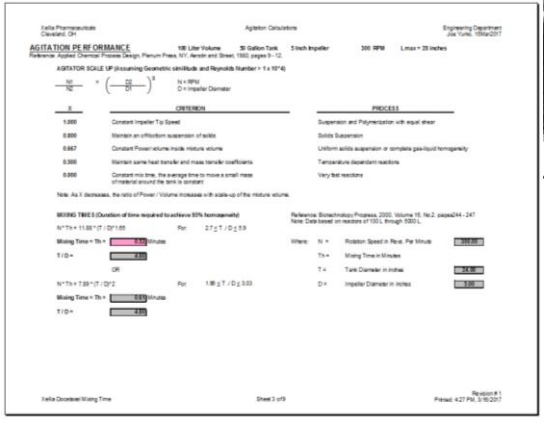
    Impeller is flat blade with magnetic coupling at tank bottom

    Photo to right shows fermenter agitator (2x flat blade turbines)
  - Blending liquids (in compounding vessels)
    - Done at low RPMs low shear
    - Less damage to structure and good mixing
  - Sparging (in compounding vessels)
    - Air or Nitrogen sparge ring at bottom of vessel
    - Done with nitrogen to drive off dissolved air in liquids and nitrogen blanket
    - Nitrogen in system prevents growth of any aerobic bacteria (product runs)
    - Air in system prevents growth of any anaerobic bacteria (media stability runs)



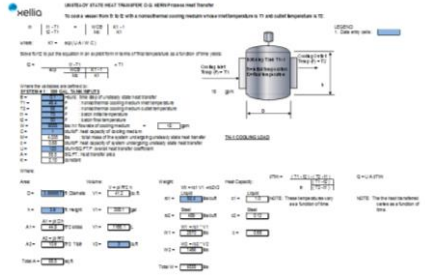


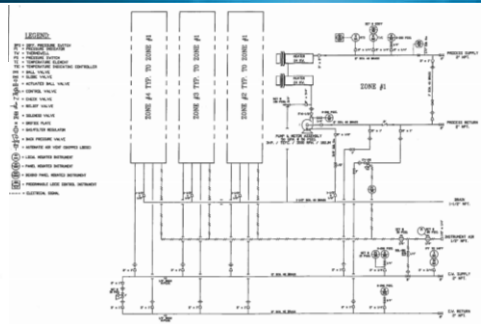


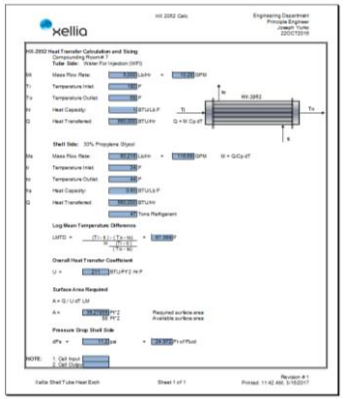


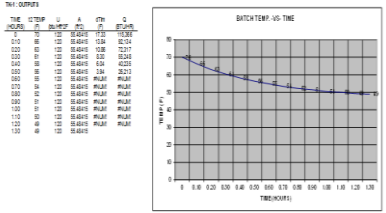
12. Process Engineering, “Lunch & Learn”

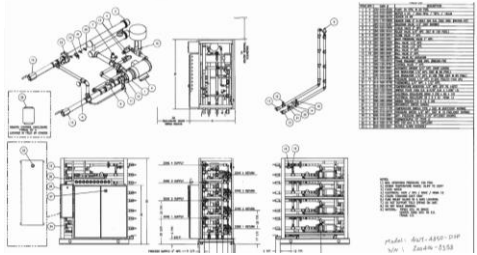
- **Heat Transfer (Parenterals)**
- Reactors/Vessels
  - Jackets are dimpled and hold 2-3 gallons
- Shell & Tube Heat Exchangers
  - High pressure operation
    - Shell side ratings: ASME pressure vessels 150 psig
    - Tube side ratings: ASME pressure rating 150 psig
  - Materials of construction
    - Clean utility: 304 to 316L SS (clean steam))
  - GMP issues
    - 2 pass tube bundle in single shell (not efficient)
      - Difficult bonnet needs drain slots to be self draining
    - 1 pass tube bundle in single shell (more efficient)
      - Slope both tube bundles needs no drain slots
  - Pressure drop shell or tube side
    - Relatively higher pressure drops
- Plate Exchangers
  - Low pressure operation
    - Plates have gaskets, can see 70 to 90 psig hot service
  - Materials of construction
    - Clean utility: 304 SS, good for utilities services
  - GMP issues
    - Plates difficult arrangement for self draining

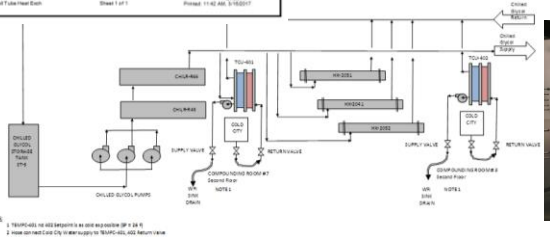


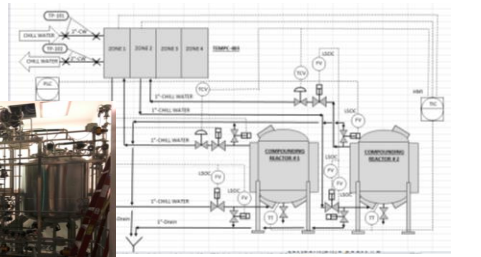












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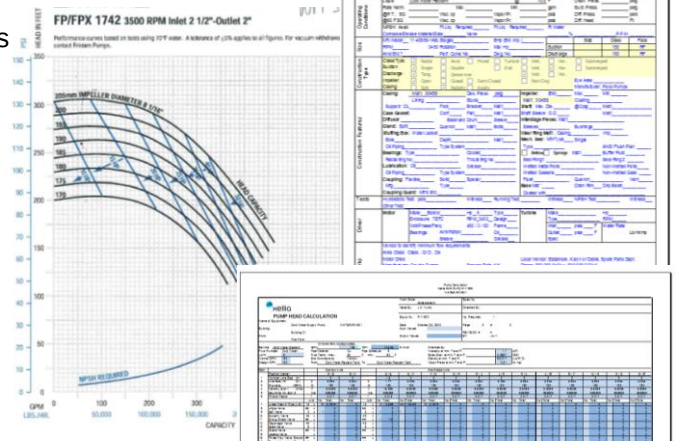
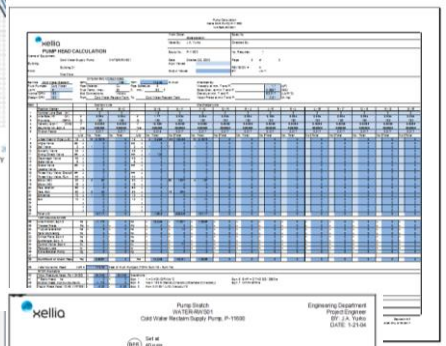
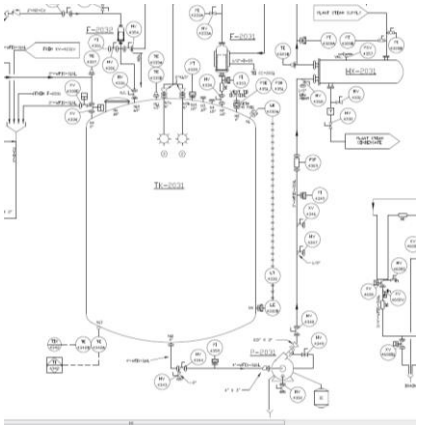
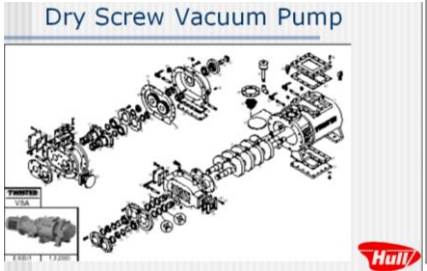
12. Process Engineering, “Lunch & Learn”

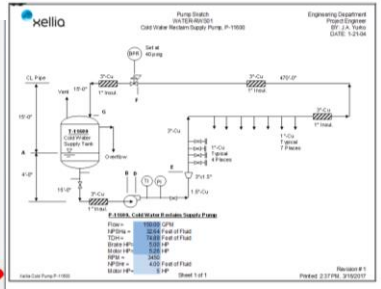
- **Pumping (Parenterals)**
  - Centrifugal Pump (watery fluids, low viscosity)
    - Continuous flow rate, high volumes, high pressure heads
    - Easily cleaned with hot water or CIP fluids
    - Materials of construction: Carbon Steel to 316L SS
    - Available in VFD or constant speed
    - Easily modified with impeller or motor Hp changes
  - Diaphragm Pump (thick fluids, medium viscosity)
    - Continuous flow rate, but pulsing flow, low volumes
    - Disassemble to clean components with hot water or CIP
    - Materials of construction plastic or 316LSS
    - Available with compressed air drive variable speed
    - Modified with air pressure or air flow rate
  - Lobe Pump (Positive Displacement, thick fluids, high viscosity)
    - Continuous flow rate, pulsing flow, low volumes, high pressure heads
    - Disassembled to clean parts, or low flow cleaning with CIP design
    - Materials of construction 316L SS
    - Available in VFD or constant speed
    - Minimal modification options
  - Vacuum Pump (thin fluids)
    - Continuous pulsing flow rate, vacuum
    - Disassemble to clean 316LSS parts











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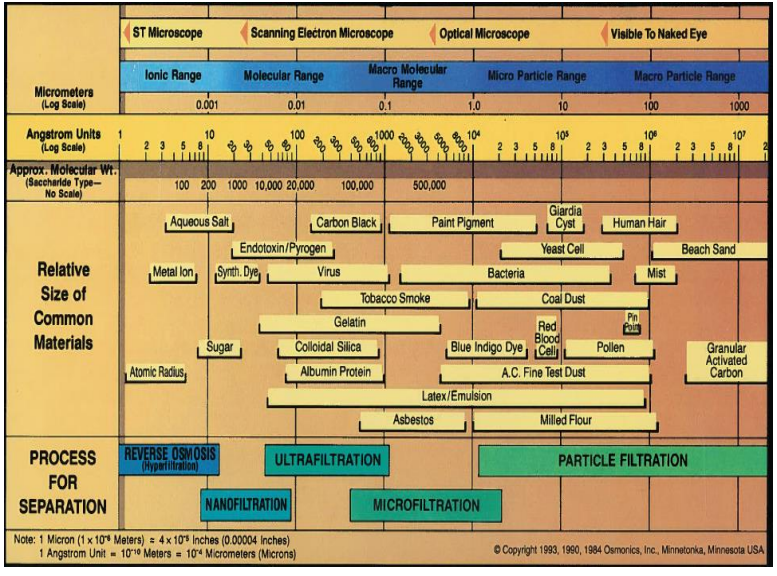
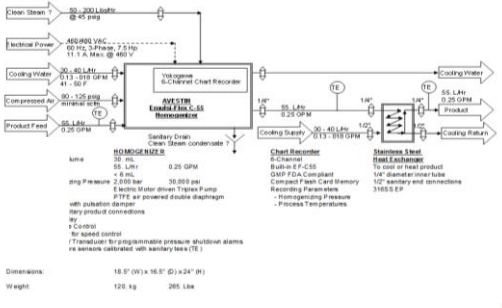
12. Process Engineering, “Lunch & Learn”

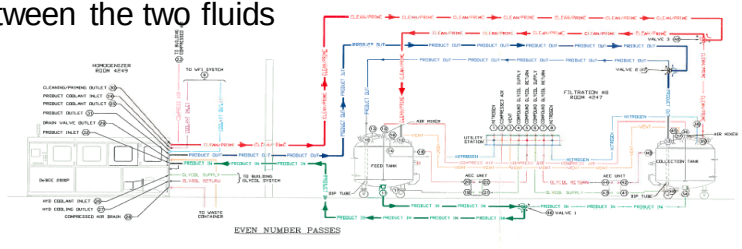
- **Filtration (Parenterals)**
  - Factors Affecting Filtration Rate
    - Pressure: Filter rate is directly proportional to the pressure difference across media
    - Viscosity: Filter rate is inversely proportional, as viscosity increases, rate decreases
    - Filter Area: Filter rate is directly proportional to the media surface area
    - Permeability Coefficient: Is a function of porosity and surface area. Filter rate is directly proportional to the media surface area.
  - Air Filtration (HEPA): 99.997% removal of particles ≥ 0.3 µm
    - Use pre-filters or roughing filters before air enters HEPA to extend life of HEPA
  - Gas or Liquids, Cartridge: Particle Filtration of particles ≥ 0.2 µm
    - Removes: Red Blood Cells, Giardia Cyst, Beach Sand
    - Micro Particle to Macro Particle Range: 1 to 1,000 µm
  - Gas or Liquids, Carbon: Volatile Organic Filtration
    - Removes: Gelatin, Bacteria, Yeast Cells
    - Molecular Range to Macro Molecular Range: 0.01 to 1.0 µm
  - Liquids, Reverse Osmosis: Hyperfiltration
    - Removes: Virus, Endotoxin/Pyrogen, Ions
    - Ionic Range to Molecular Range: 0.0001 to 0.01 µm



12. Process Engineering, “Lunch & Learn”

- **Size Reduction, Homogenizers (Parenterals)**
  - Microencapsulation: API covered with Lipid
    - Propofol: Very effective general anaesthetic, acts within minutes and recovery within minutes with no nausea. As a parenteral it is able to pass the blood-brain barrier since the microscopic API droplet has a lipid coating
  - Particle Size Distribution: Critical to have narrow distribution with most micro-particles the same size
  - Effective component design: Precision Flow Orifice
    - Under high pressure flow conditions steams of API and Lipid mix and flow through a Flow Orifice with a micro-sized opening causing the API to be coated by the lipid as a function of surface tension between the two fluids





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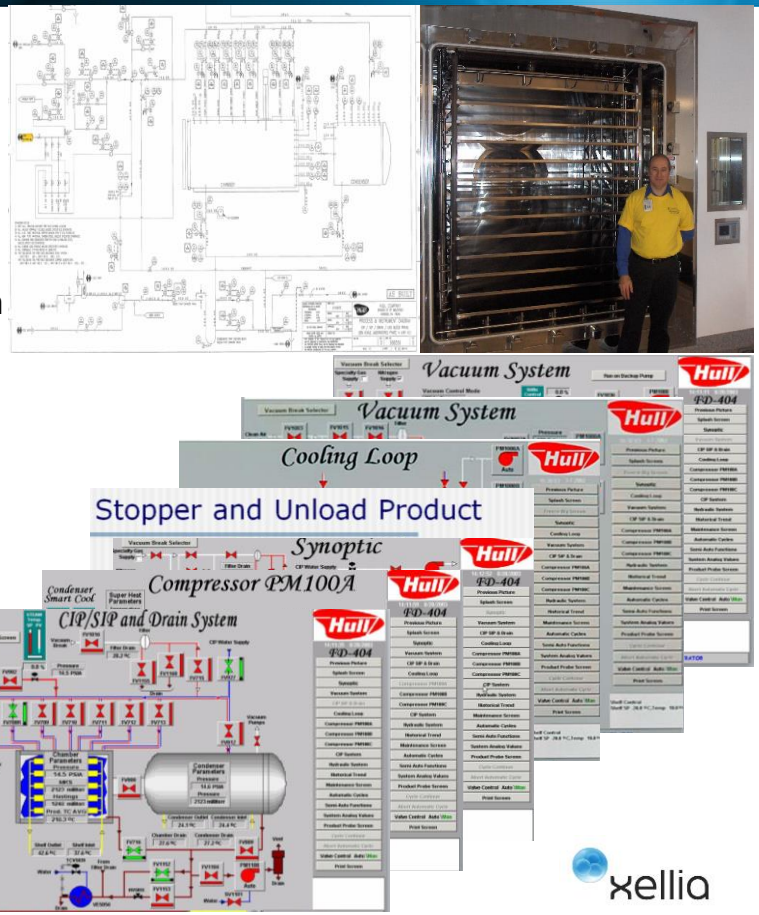
12. Process Engineering, “Lunch & Learn”

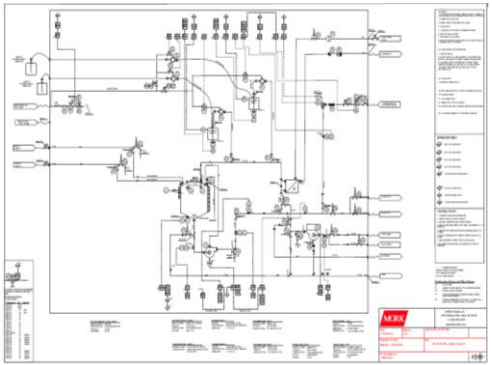
- **Freeze Drying (Lyophilization)**
  - Extreme form of vacuum drying. Solid is frozen and drying is done via subliming the solid phase
  - Temperature conditions are -50°C, and Pressure conditions are 0.2 Torr
  - Most expensive method of drying. Done in large batches (freezer shelf area = 400 sq.ft.)
  - Freeze Dry product when product experiences high rates of decomposition at STP
  - Product shelf life is extended from 1 week to 2 years
  - Freeze Dryer Loading, Sealing, and Vacuum
  - Freezing occurs in three stages after vial contents is a solid in the vacuum
    - Freezing (Thermal Treatment): Mixture in vial freezes completely (minutes)
    - Primary Drying (Sublimation): Surface free solid water sublimates (hours), risk “meltback” if product warms
    - Secondary Drying (Desorption/Diffusion): Crystalline trapped solid water diffuses to sublimate (days)
  - Freeze Dryer Stoppering and Pressurization
    - At the end of the freeze drying cycle the shelves are compressed to press the stoppers into the vials
    - The freeze dryer chamber is re-pressurized with Nitrogen to restore the atmospheric level pressure
  - Unloading
  - Cleaning and Steaming
    - Clean In Place (CIP) with WFI and / or CIP 100 (acid) and / or CIP 200 (caustic0
    - Steam In Place (SIP) with Clean Steam for qualified time and temperature lethality exposure

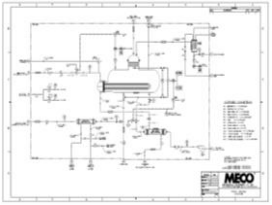


12. Process Engineering, “Lunch & Learn”

- **Distillation** (Vapor Compression Distillation)
  - Receive feed water from the Reverse Osmosis unit to vapor compression distillation unit
  - Feed water is vaporized from 55 psig plant steam with shell & tube heat exchanger
  - Shell side vaporized water is compressed and condensed as a hot pure liquid WFI

- **Clean-In-Place** (CIP), or **Clean-Out of-Place** (COP)
  - Piping systems are sloped with no pockets and no dead-legs
  - Temperatures 180°F (80°C), not less than 170°F (77°C)
  - Collected WFI post rinse water is collected as pre-rinse water
  - Steris CIP-100 (acidic) and CIP-200 (basic) solutions are rinsed
  - Post rinse WFI water is final rinse of system (event step, pH monitor)
  - Piping systems are velocity cleaned, turbulent 5-8 feet per second
    - Must have sufficient time for drain down between 3 phases of cleaning
  - Vessel systems are pressure cleaned, need 120 psig jet pressure from spray ball or jet
    - No liquid level buildup in vessel to prevent covering surface from cleaning jets





- **Steam-In-Place** (SIP)
  - Piping systems are sloped with no pockets and no dead-legs
  - Flush vessels for 10 minutes with 10 volumes of steam to remove non-condensables
  - Provide steam traps before entry into equipment to provide saturated dry steam for SIP
  - Contact time of 20 minutes at a temperature of 265°F (129 °C) will provide lethality for a 3-6 log reduction in CFUs

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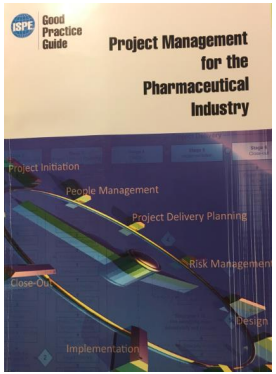
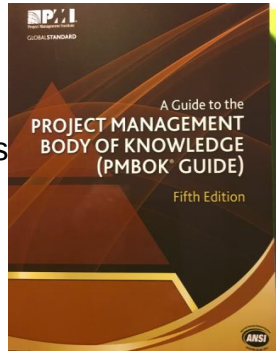
12. Process Engineering, “Lunch & Learn”

- **Project Management Issues**
- **Capital Costs**
  - Process equipment needs must be determined before developing an accurate capital cost estimate for a pharmaceutical manufacturing facility or any single process contained in such facility
  - Define the needs of process equipment, support equipment, utility equipment, the building and the site needs
  - In early project planning, historical square footage costs are often used
  - The cost per square foot of a process facility normally falls in a reasonable range ($500 to $2,000 per sq. ft.)
  - Depending on the size and type of the process it is difficult to quickly determine the square footage required
  - The process engineer must define the process equipment needed to meet the production objectives, participate in discussions on equipment layouts, and estimate the utility requirements for their layouts
- **Project Schedules**
  - Most projects have the delivery of the equipment to the construction site as the critical path
  - Some equipment may take from 5 to 15 months to fabricate, have the FAT, and then ship with all documents
  - The process engineer must size and specify (URS) the equipment quickly to contracts can go to three bidders and an award can be made to the best qualifying vendor (based on work quality, delivery time, and cost)
  - The vendor engineering can then be performed, equipment can be fabricated, and the FAT may be done
  - When equipment is completed and shipping it must be easily located into the facility that is mostly complete
  - The equipment must then be integrated into the facility architecture, piping, and instrumentation automation
  - At this point the Site Acceptance Testing (SAT) may begin as commissioning leading up to validation





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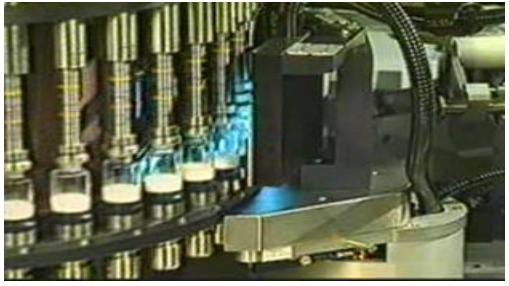
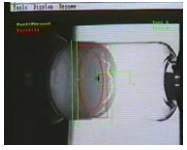
12. Process Engineering, “Lunch & Learn”

- **Reference Materials**
  - Good Design Practices for GMP Pharmaceutical Facilities, Volume 214, 2nd Edition, CRC Press, Terry Jacobs, AIA, Andrew A. Signore, PE
  - Pharmaceutical Process Engineering, Volume 112, Drugs and the Pharmaceutical Sciences, Anthony J. Hickey, David Ganderton
  - Clean-In-Place for Biopharmaceutical Processes, Drugs and the Pharmaceutical Sciences, Volume 173, Dale A. Seiberling
  - Freeze-Drying/Lyophilization of Pharmaceutical and Biological Products, 2nd Ed. Drugs and the Pharmaceutical Sciences, Volume 137, Louis Rey, Joan C. May
  - Microencapsulation, Methods and Industrial Applications, 2nd Ed. Drugs and the Pharmaceutical Sciences, Volume 158, Simon Benita
  - Filtration in the Pharmaceutical Industry, Advances in Parenteral Sciences, Marcel Dekker, Inc., Theodore H. Meltzer
  - Pall Solutions for the BioPharmaceutical Industry, Pall Life Sciences Catalog
  - Cleanroom Design, John Wiley& Sons, W. Whyte
  - Flow of Fluids, Crane, Technical Paper No. 410





Spring Semester Internship Partnership In Summary

Internship Project Weekly Status Report, Milestones

CWRU selects 12 companies in Greater Cleveland Area to host 4 interns

- Week 1 Scope of Work, Schedule, Deliverables, and Contract for Project
- Week 2 Orientation to Pharmaceutical Standards and Project Management
- Week 3 Develop Scope of Work for the Request For Quotation
- Week 4 Review / Approve Scope of Work (PFDs, Data Sheets…etc.)
- Week 5 Three vendors to quote cost & delivery on equipment fabrication (2 weeks)
- Week 6 Draft midterm presentation with vendor quote Bid Tabulation (if available early)
- Week 7 **Midterm** Presentation (add 3 vendor quotes if available)
- Week 8 Develop Scopes of Work for the Automation and Installation
- Week 9 Review / Approve Scopes of Work for Automation and Installation
- Week 10 Automation RFQ and Installation RFQ: three vendors to quote (2 weeks)
- Week 11 Evaluate Formulation Process Steps on WFI Process Optimization Simulation
- Week 12 Draft final presentation with Automation & Installation vendor quote Bid Tab.
- Week 13 **Final** Presentation, Turn Over Package & Lessons Learned

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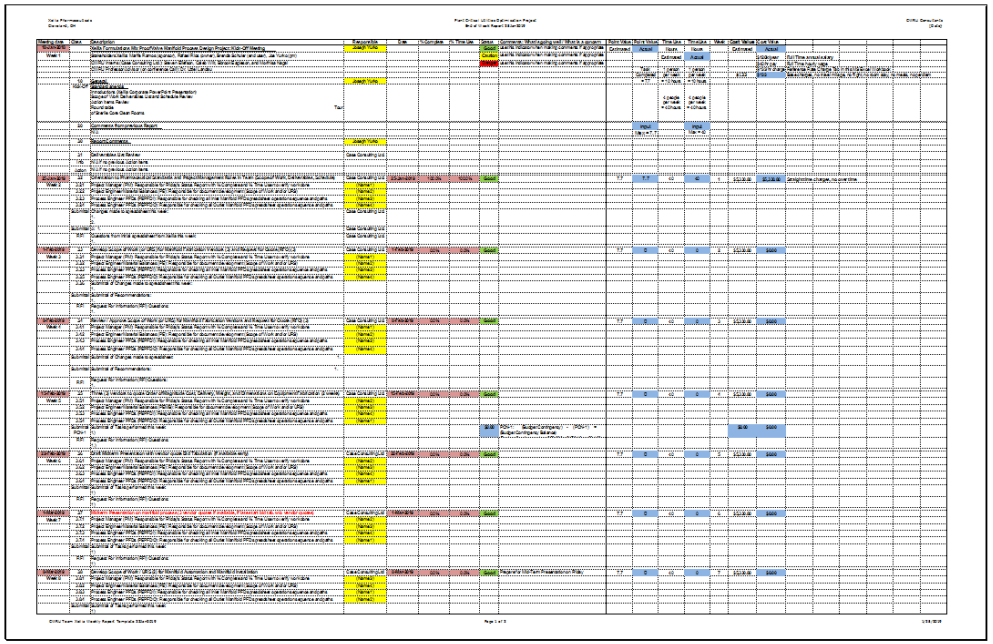
Spring Semester Internship Partnership Weekly Meetings

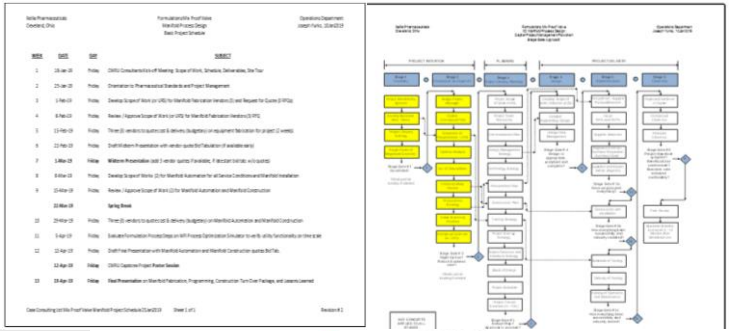
- **Weekly Status Report Conference Calls (PM)**
  - Submittal of Deliverables
  - Request For Information (RFI)
  - Deliverables In Progress Status
  - Transmittal List of Documents Update
  - Project Management KPI Work Percent Complete
  - Project Management KPI Mandays Percent Used
  - Project Change Notice Request and/or Approval

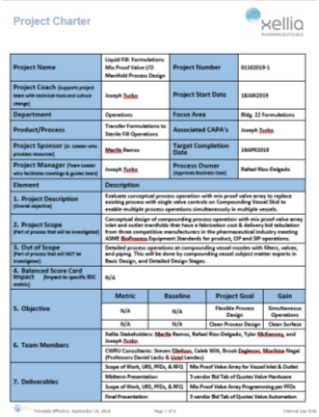


- **Project Management Role Rotation**
  - Every 3 weeks rotate roles in team
  - Project Manager, Project Engineer, and Process Engineers
  - Weekly status report, Documents, and PFDs

Spring Semester Internship Partnership Week 1

- **Week 1 Charter, Scope of Work, Deliverables, Schedule, and Contract for Project**
  - Project Charter
  - Scope of Work
  - Deliverables
  - Schedule
  - Contract
  - Billing Rate
  - NDA





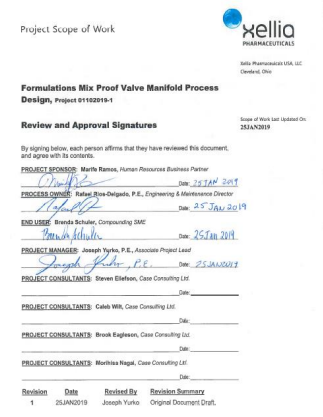
Project Charter

Project Name	Liquid Fill: Formulations Mix Proof Valve I/O Manifold Process Design	Project Number	01102019-1
Project Coach	Joseph Yurko	Project Start Date	1JAN2019
Department	Operations	Focus Area	Bldg. 22 Formulations
Product/Process	Transfer Formulations to Sterile Fill Operations	Associated CAPA's	Joseph Yurko
Project Sponsor	Marife Ramos	Target Completion Date	18APR2019
Project Manager	Joseph Yurko	Process Owner	Rafael Rios-Delgado

Element	Description
1. Project Description	Evaluate conceptual process operation with mix proof valve array to replace existing process with single valve controls on Compounding Vessel Skid to enable multiple process operations simultaneously in multiple vessels.
2. Project Scope	Conceptual design of compounding process operation with mix proof valve array inlet and outlet manifolds that have a fabrication cost & delivery bid tabulation from three competitive manufacturers in the pharmaceutical industry meeting ASME BioProcess Equipment Standards for product, CIP and SIP operations.
3. Out of Scope	Detailed process operations at compounding vessel nozzles with filters, valves, and piping. This will be done by compounding vessel subject matter experts in Basic Design, and Detailed Design Stages.
4. Balanced Score Card Impact (Impact to specific BSC metric)	N/A

5. Objective	Metric	Baseline	Project Goal	Gain
	N/A	N/A	Flexible Process Design	Simultaneous Operations
	N/A	N/A	Clean Process Design	Clean Surface

6. Team Members	Xellia Stakeholders: Marife Ramos, Rafael Rios-Delgado, Tyler McKeeany, and Joseph Yurko CWRU Consultants: Steven Ellefson, Caleb Will, Brook Eagleson, Marihisa Nagai (Professors Daniel Lacks & Lizet Lerebro)
7. Deliverables	Scope of Work, URS, PFDs, & BFQ Mix Proof Valve Array for Vessel Inlet & Outlet Midterm Presentation 3 vendor Bid Tab of Quotes Value Hardware Value of Work: URS, PFDs, & BFQ Mix Proof Valve Array Programming per PFDs Final Presentation: 3 vendor Bid Tab of Quotes Value Automation



Project Scope of Work

Formulations Mix Proof Valve Manifold Process Design, Project 01102019-1

Review and Approval Signatures

By signing below, each person affirms that they have reviewed this document, and agree with its contents.

PROJECT SPONSOR: **Marife Ramos**, *Human Resources Business Partner*
Date: 25JAN 2019

PROCESS OWNER: **Rafael Rios-Delgado, P.E.**, *Engineering & Maintenance Director*
Date: 25 JAN 2019

END USER: **Brenda Schuler**, *Compounding SME*
Date: 25Jan 2019

PROJECT MANAGER: **Joseph Yurko, P.E.**, *Associate Project Lead*
Date: 25JAN2019

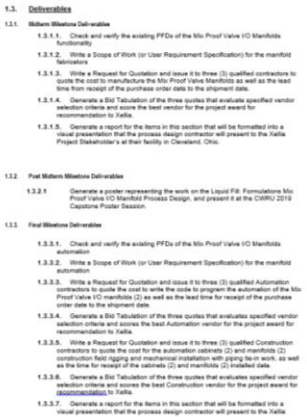
PROJECT CONSULTANTS: **Steven Ellefson**, *Case Consulting Ltd.*
Date:

PROJECT CONSULTANTS: **Caleb Will**, *Case Consulting Ltd.*
Date:

PROJECT CONSULTANTS: **Brook Eagleson**, *Case Consulting Ltd.*
Date:

PROJECT CONSULTANTS: **Morihisa Nagai**, *Case Consulting Ltd.*
Date:

Revision	Date	Revised By	Revision Summary
1	25JAN2019	Joseph Yurko	Original Document Draft.



1.3. Deliverables

1.3.1. Midterm Milestone Deli-erables

1.3.1.1. Check and verify the existing PFDs of the Mix Proof Valve I/O Manifolds functionality

1.3.1.2. Write a Scope of Work (or User Requirement Specification) for the manifold fabrications

1.3.1.3. Write a Request for Quotation and issue it to three (3) qualified contractors to quote the cost to manufacture the Mix Proof Valve Manifolds as well as the lead time from receipt of the purchase order date to the shipment date.

1.3.1.4. Generate a Bid Tabulation of the three quotes that evaluates specified vendor selection criteria and scores the best vendor for the project award for recommendation to Xellia.

1.3.1.5. Generate a report for the items in this section that will be formatted into a visual presentation that the process design contractor will present to the Xellia Project Stakeholder's at their facility in Cleveland, Ohio.

1.3.2. Post Midterm Milestone Deli-erables

1.3.2.1 Generate a poster representing the work on the Liquid Fill: Formulations Mix Proof Valve I/O Manifold Process Design, and present it at the CWRU 2019 Capstone Poster Session.

1.3.3. Final Milestone Deli-erables

1.3.3.1. Check and verify the existing PFDs of the Mix Proof Valve I/O Manifolds automation

1.3.3.2. Write a Scope of Work (or User Requirement Specification) for the manifold automation

1.3.3.3. Write a Request for Quotation and issue it to three (3) qualified Automation contractors to quote the cost to write the code to program the automation of the Mix Proof Valve I/O manifolds (2) as well as the lead time for receipt of the purchase order date to the shipment date.

1.3.3.4. Generate a Bid Tabulation of the three quotes that evaluates specified vendor selection criteria and scores the best Automation vendor for the project award for recommendation to Xellia.

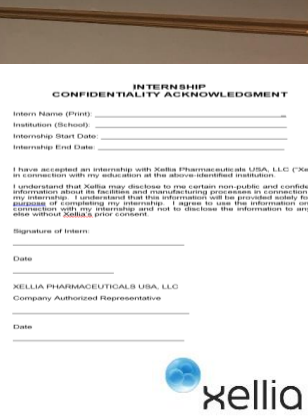
1.3.3.5. Write a Request for Quotation and issue it to three (3) qualified Construction contractors to quote the cost for the automation cabinets (2) and manifolds (2) construction fast rigging and mechanical installation with piping tie-in work, as well as the time for receipt of the cabinets (2) and manifolds (2) installed date.

1.3.3.6. Generate a Bid Tabulation of the three quotes that evaluates specified vendor selection criteria and scores the best Construction vendor for the project award for recommendation to Xellia.

1.3.3.7. Generate a report for the items in this section that will be formatted into a visual presentation that the process design contractor will present to the Xellia

CWRU Consultants Hypothetical Hourly Charge For Project Management KPI

ITEM	DESCRIPTION	VALUE	COMMENTS
1	AIChE 2017 Salary Survey: Annual	$120,000	For Consulting Engineer
2	Take Home Hourly Rate	$57.69	52 week year, 5 day week, 8 hr day
3	Annual Social Security, Medicare & Tax	$120,000	For Consulting Engineer
4	Take Home & Taxes Hourly Rate	$115.38	With Social Security, Medicare & Tax
5	Profit (5%) Hourly Rate	$121.15	With Profit Multiplier
6	Insurance, Office, utilities, supplies (10%)	$133.27	With Operating Cost Multiplier
7	15 Week (40 hr/week) project cost	$79,961.54	Based on straight time hourly rate
8	**Total Project Estimated Budgeted Value**	**$80,000**	**Based on Lump Sum Project Award**



INTERNSHIP
CONFIDENTIALITY ACKNOWLEDGMENT

Intern Name (Print): _____

Institution (School): _____

Internship Start Date: _____

Internship End Date: _____

I have accepted an internship with Xellia Pharmaceuticals USA, LLC ("Xellia") in connection with my education at the above-identified institution.

I understand that Xellia may disclose to me certain non-public and confidential information about its facilities and manufacturing processes in connection with my internship. I understand that this information will be provided solely for the purpose of completing my internship. I agree to use this information only in connection with my internship and not to disclose the information to anyone else without Xellia's prior consent.

Signature of Intern: _____

Date _____

XELLIA PHARMACEUTICALS USA, LLC

Company Authorized Representative

_____

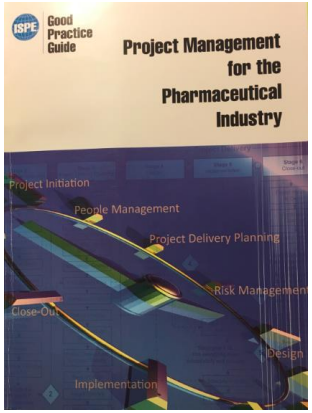
Date

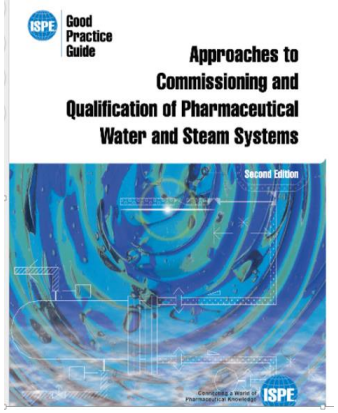
_____

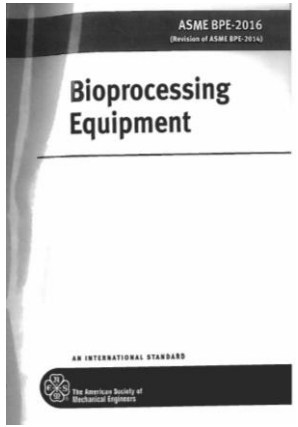
xellia

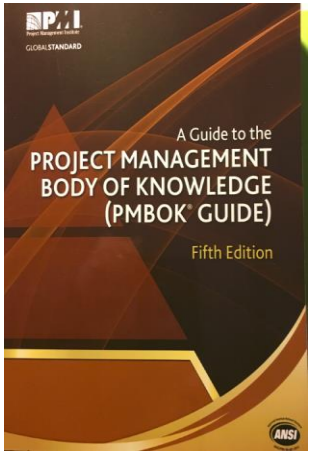
Spring Semester Internship Partnership Week 2

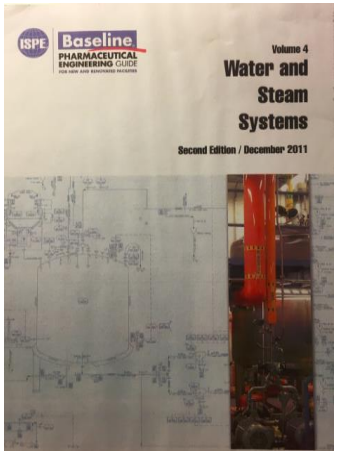
- **Week 2 Orientation to Pharmaceutical Standards and Project Management**
  - American Society of Mechanical Engineers (ASME)
    - ASME BioProcess Equipment Standard
  - International Society for Pharmaceutical Engineers (ISPE)
    - ISPE Baseline Guides: Water For Injection &, Clean Steam
    - ISPE Good Engineering Practices
    - ISPE Project Management for the Pharmaceutical Industry
  - Project Management Professional (PMP) Standard
    - Project Management Body Of Knowledge

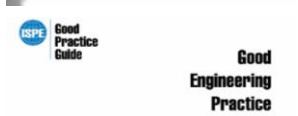












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Spring Semester Internship Partnership Week 3

- **Week 3 Develop Scope of Work for the Request For Quotation (RFQ)**
  - Scope of Work (or User Requirement Specification)
  - Request for Quotation (RFQ)

Project Scope of Work

xellia PHARMACEUTICALS

Xellia Pharmaceuticals USA, LLC
Cleveland, Ohio

Formulations Mix Proof Valve Manifold Process Design, Project 01102019-1

Scope of Work Last Updated On:
25JAN2019

Review and Approval Signatures

By signing below, each person affirms that they have reviewed this document, and agree with its contents.

PROJECT SPONSOR: **Marife Ramos,** *Human Resources Business Partner*
Date: 25 JAN 2019

PROCESS OWNER: **Rafael Rios-Delgado, P.E.,** *Engineering & Maintenance Director*
Date: 25 JAN 2019

END USER: **Brenda Schuler,** *Compounding SME*
Date: 25 Jan 2019

PROJECT MANAGER: **Joseph Yurko, P.E.,** *Associate Project Lead*
Date: 25JAN2019

PROJECT CONSULTANTS: **Steven Ellefson,** *Case Consulting Ltd.*
Date:

PROJECT CONSULTANTS: **Caleb Wilt,** *Case Consulting Ltd.*
Date:

PROJECT CONSULTANTS: **Brook Eagleson,** *Case Consulting Ltd.*
Date:

PROJECT CONSULTANTS: **Morihisa Nagai,** *Case Consulting Ltd.*
Date:

Revision	Date	Revised By	Revision Summary
1	25JAN2019	Joseph Yurko	Original Document Draft.

Project Definition

1.1. Background

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A process design contractor will be selected to perform a Conceptual Design for a Formulations Mix Proof Valve I/O Manifold Process. This design will be done to improve the cGMP flexibility of performing multi-process operations on multiple formulation vessels simultaneously. It is also required to improve the cGMP functionality of the process design to reduce the time to efficiently clean the exterior surfaces of the valves, fittings, and piping on the formulation vessels considering the pneumatic tubing bundles as well as the I/O signal wiring for the valve positioner limit switches.

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The existing process design of valves, fittings, and piping on the inlet and outlet of the two Formulation Vessels provides very limited flexibility between the two vessels when considering simultaneous operations on the two vessels with multiple service operations. This would not permit the CIP or SIP on one vessel when formulating on the second vessel. There is not sufficient double block and bleed protection between the utility services on the piping inlet and outlet of the vessels.

It is recommended that the majority of the service piping inlet and outlet to the two vessels have the existing double block and bleed valves be replaced with mix proof valve inlet and outlet manifolds. The manifolds will be sloped one percent such that they will be self-draining with no liquid hold up.

These manifolds will meet the ASME BioProcess Equipment Standard for the materials of construction (316L Stainless Steel) as well as the surface finish of 20 Ra or better for the product contact surfaces. The elastomers to be used must meet the thermal exposure of clean steam for 30 minutes or less.

The actuation of the rising stem mix proof valve must have pneumatic control to open with instrument air, and when not active have a spring return to close. The automation rising stem mix proof valve must also have limit switches that will signal the valve is in the open or closed position as feedback signal communication with the process automation control system.

For this project Midterm Milestone the process design contractor will check and verify the functionality of the existing process flow diagrams of the Mix Proof Valve I/O Manifolds (2), write a Scope of Work and/or a User Requirement Specification for manifold fabrication contractors. The process design contractor will also write a Request for Quotation and issue it to three (3) qualified contractors for a budgetary quote for the cost to manufacture the Mix Proof Valve I/O Manifolds (2) for all the PFD service conditions, as well as the lead time from receipt of the purchase order date to the shipment date.

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The process design contractor will take the collected results from above and process it into a report formatted into a visual presentation to the Xellia Project Stakeholder's at their facility in Cleveland, Ohio. This will complete the first milestone on this project.

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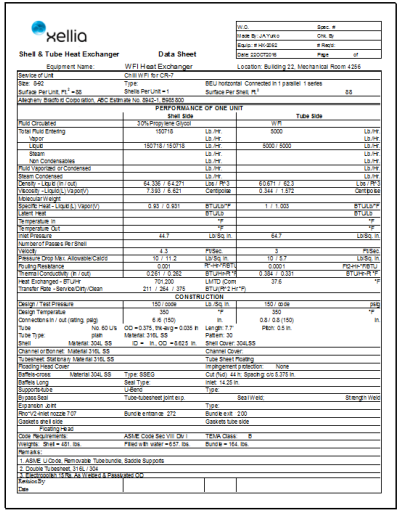
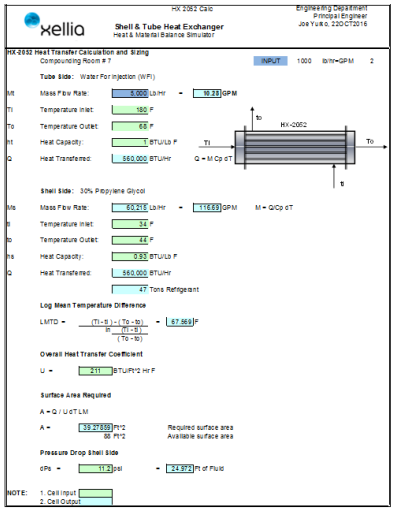
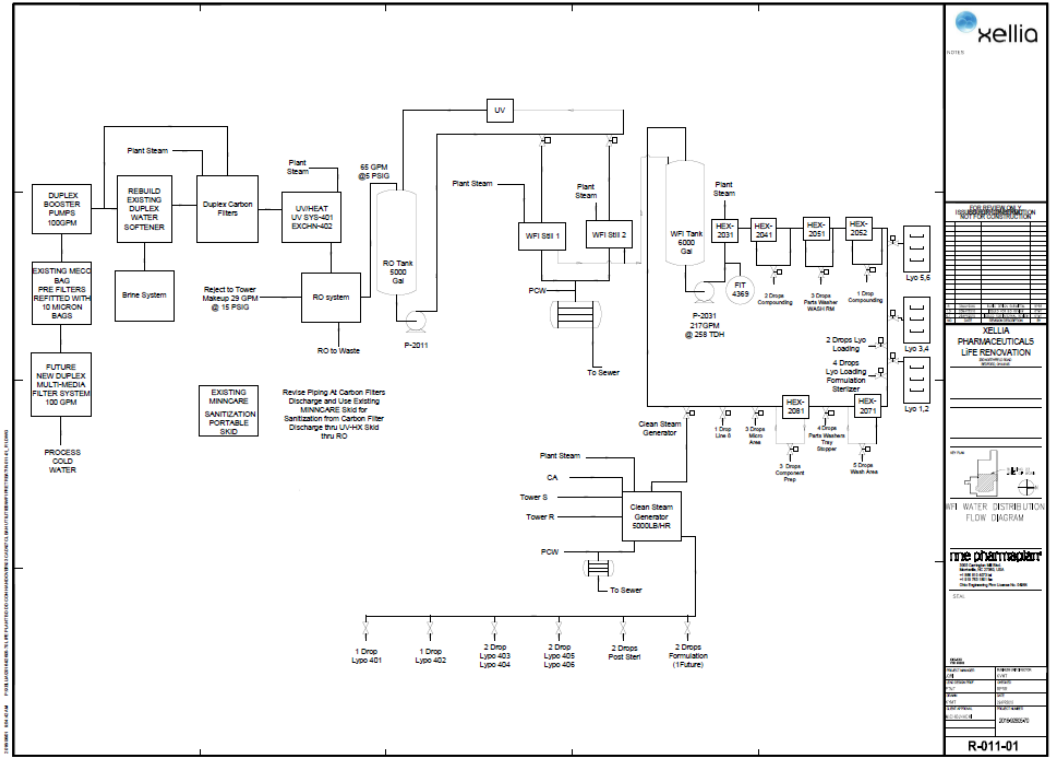
Spring Semester Internship Partnership Week 4

- **Week 4 Review / Approve Scope of Work (PFDs, Data Sheets…etc.)**
  - Scope of Work (or URS)
  - Process Flow Diagrams (PFDs)
  - Equipment Data Sheets
  - ASME BPE Specifications







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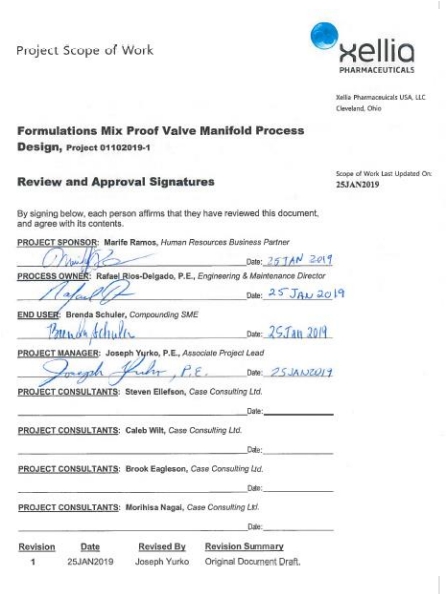
Spring Semester Internship Partnership Week 5

- **Week 5 Request For Quotation (RFQ) from three vendors to quote cost (order of magnitude +/- 30%) & delivery on Manifold fabrication (2 weeks)**
  - Cost (order of magnitude +/- 30%) & Delivery Quote Vendors 1-3
  - Include approximate weights of major components for installation
  - Include approximate dimensions of equipment for installation



Project Scope of Work

xellia PHARMACEUTICALS

Xellia Pharmaceuticals USA, LLC
Cleveland, Ohio

Formulations Mix Proof Valve Manifold Process Design, Project 01102019-1

Review and Approval Signatures

Scope of Work Last Updated On: 25JAN2019

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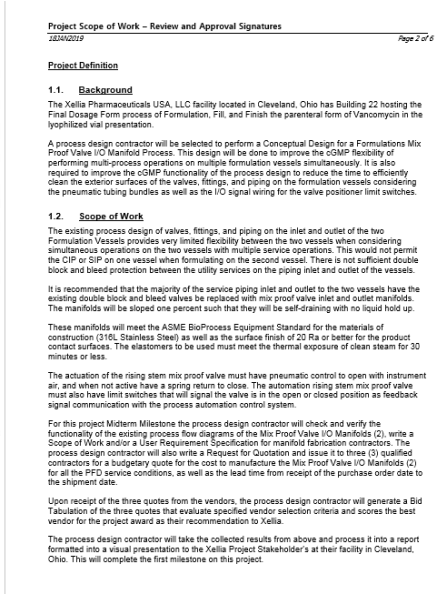

Project Scope of Work – Review and Approval Signatures
18JAN2019 Page 2 of 6

Project Definition

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Spring Semester Internship Partnership Week 6

- **Week 6 Draft midterm presentation with three Manifold vendor quotes in Bid Tabulation format (if available early)**
  - Manifold Quote Bid Tabulation for 3 Vendors
  - Include Engineering Estimates for comparison
  - Develop vendor scoring method criteria for comparison evaluation

Xellia Pharmaceuticals
Cleveland, Ohio

Liquid Fill Formulations Mix Proof Valve
I/O Manifold Process Design
Manifold Vendor Bid Tabulation

Operations Department
Joseph Yurko, 10Jan2019

VENDOR CRITERIA	Engineering Est	INOXPA	INOXPA Comments	Tuchenhagen	Tuchenhagen Comments	Cherry Burrell	Cherry Burrell Comments
Mix Proof Valve Manifolds							
Inlet Mix Proof Valve Manifold							
Unit Cost	$ 108,000	$38,000	Quote. No Solenoid Cab	$1	Quote. No Solenoid Cab	$1	Quote. No Solenoid Cab
Added Cost (tax, S&H)	$21,600	$7,600		$0		$0	
Drawing Delivery ARO	1 to 2 Weeks	1 to 2 Weeks	Long Delivery	2 to 3 Weeks	Long Delivery	3 to 4 Weeks	Long Delivery
Manifold Delivery ARO	15 to 16 Weeks	15 to 16 Weeks	Long Delivery	22 to 24 Weeks	Long Delivery	TBD at time of order Weeks	Long Delivery
Score	19	19	Ship from Spain (customs)	10	Ship from Spain (customs)	2	Ship from Spain (customs)
Outlet Mix Proof Valve Manifold							
Unit Cost	$ 108,000	$27,120	Quote. No Solenoid Cab	$1	Quote. No Solenoid Cab	$1	Quote. No Solenoid Cab
Added Cost (tax, S&H)	$21,600	$5,424		$0		$0	
Drawing Delivery ARO	1 to 2 Weeks	NA	Long Delivery	2 to 3 Weeks	Long Delivery	3 to 4 Weeks	Long Delivery
Manifold Delivery ARO	15 to 16 Weeks	NA	Long Delivery	22 to 24 Weeks	Long Delivery	TBD at time of order Weeks	Long Delivery
Score	19	19	Ship from Spain (customs)	10	Ship from Spain (customs)	2	Ship from Spain (customs)
Inlet Manifold Automation							
Unit Cost	$32,400	$1	Quote. No Programming	$1	Quote. No Programming	$1	Quote. No Programming
Added Cost (tax, S&H)	$6,480	$0		$0		$0	
Code Description Delivery ARO	1 to 2 Weeks	NA	Delivery Time Not Quoted	N/A	Delivery Time Not Quoted	NA	Delivery Time Not Quoted
Code Programming Delivery ARO	15 to 16 Weeks	NA	Delivery Time Not Quoted	N/A	Delivery Time Not Quoted	NA	Delivery Time Not Quoted
Score	2	2	Ship from Spain (customs)	2	Ship from Spain (customs)	2	Ship from Spain (customs)
Outlet Manifold Automation							
Unit Cost	$32,400	$1	Quote. No Programming	$1	Quote. No Programming	$1	Quote. No Programming
Added Cost (tax, S&H)	$6,480	$0		$0		$0	
Code Description Delivery ARO	1 to 2 Weeks	NA	Delivery Time Not Quoted	N/A	Delivery Time Not Quoted	NA	Delivery Time Not Quoted
Code Programming Delivery ARO	8 to 9 Weeks	NA	Delivery Time Not Quoted	N/A	Delivery Time Not Quoted	NA	Delivery Time Not Quoted
Score	2	2	Ship from Spain (customs)	2	Ship from Spain (customs)	2	Ship from Spain (customs)
Company Insurance & bonding							
Score	8	8		8		8	
Total Cost	$336,960	$76,146	Minimum Cost	$5	Average Cost	$8	Maximum Cost
Total Score	50	50		32		16	
% Difference (Basis: Lowest Quote)	NA	76.61% Best Quote		100.00% Mid Quote		100.00% Worst Quote	
VENDOR CRITERIA						SCORING CRITERIA (points: best, medium, worst)	
1. Only bid 3 relatively same-sized contractors							
2. Pre-bid meeting to request for a legitimate bid						10, 5, 1	Cost relative to Engr. Est.
3. Deal with the exceptions to put the quotations on the same plane							
4. Generate your own independent engineering estimate						9, 5, 1	Delivery with Customs Time
5. Order the quotes from lowest to highest and place your estimate in this ranking							
6. If the design house estimate does not fall within the spread, discuss it with them						8, 0, 0	Xellia Qualified & Bonded
7. Meet with each contractor to go over the scope one more time, to compare their estimates to yours, and to negotiate the price if required							
8. Award the job to whom you can best justify doing so.						7, 4, 1	Xellia experience with vendor
9. Reference Vessel Data Sheets for design details/specifications (issued to all vendors for quotation's basis)							
						6, 3, 1	Vendor reputation (D&B)
LEGEND:							
Red Letters or shaded cell denotes concern						Sum Total for three quotes	Quote totals rank's score
AR Value = $250,000 to $300,000							Recommend Highest Score
						https://www.dnb.com/products	Verify Dunn & Bradstreet Ranking

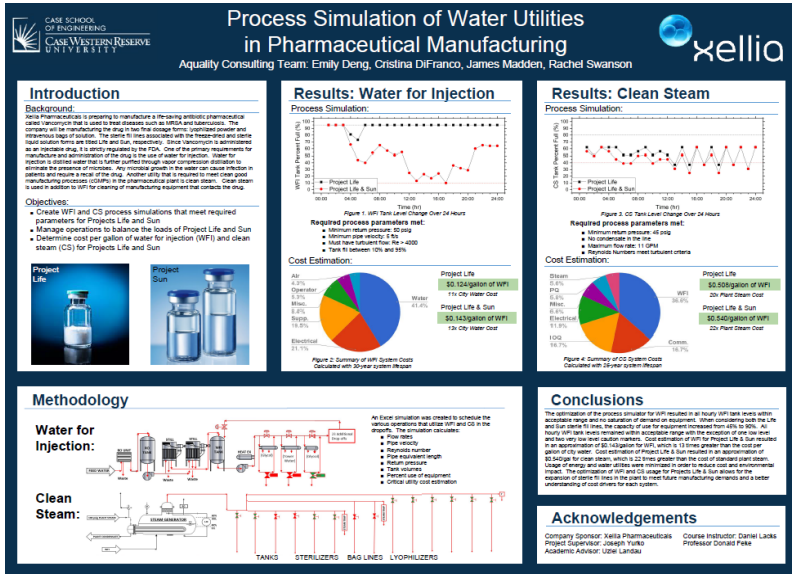
Mix Proof Valve Manifold Vendor Bid Tab Rev 1

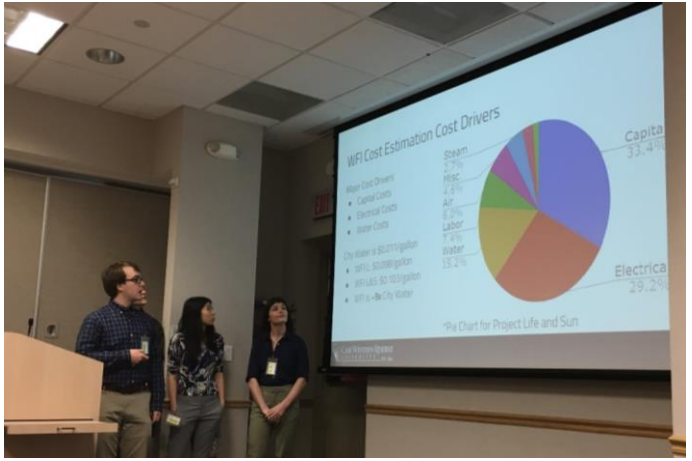
Sheet 1 of 1

Revision # 1
Printed: 3:45 PM, 1/22/2019

Spring Semester Internship Partnership Week 7

- **Week 7 Midterm Presentation (with 3 vendor quotes if available) and CWRU Capstone Poster Presentation**
  - Midterm Presentation
    - MS PowerPoint Presentation (30 minutes plus 15 minutes Q&A)
  - Capstone Poster Presentation
    - CWRU Campus College wide poster presentations





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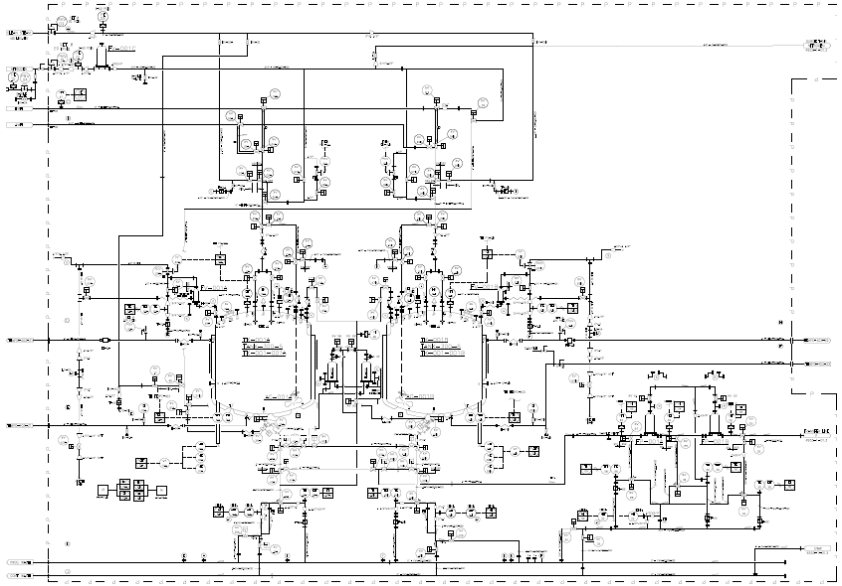
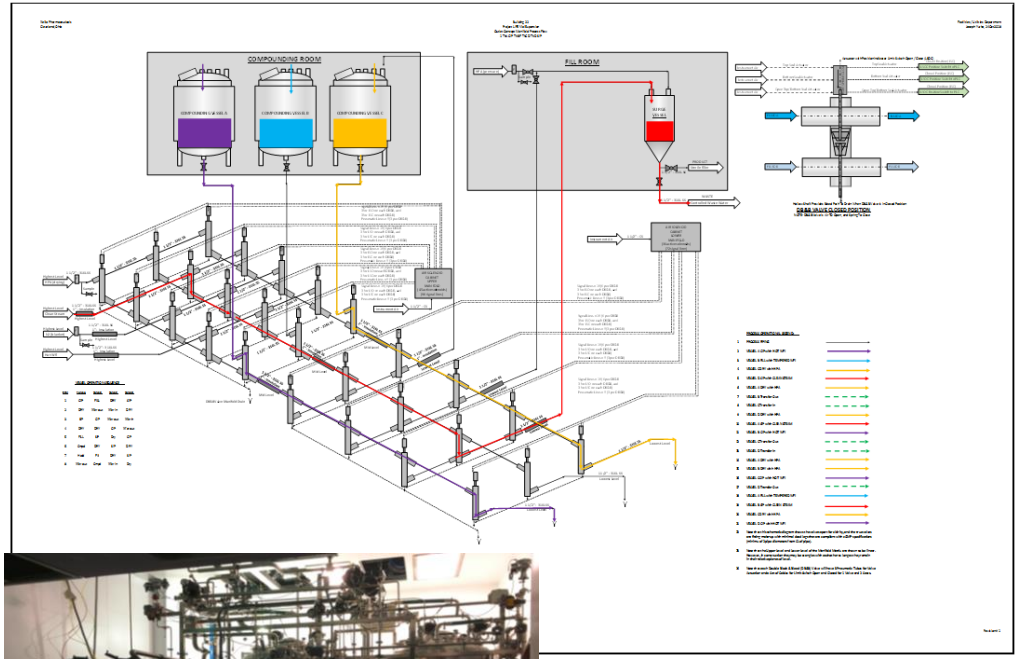
Spring Semester Internship Partnership Week 8

- **Week 8 Develop Scopes of Work for the Automation and Installation (constructability)**
  - Automation Scope of Work
  - Installation Scope of Work





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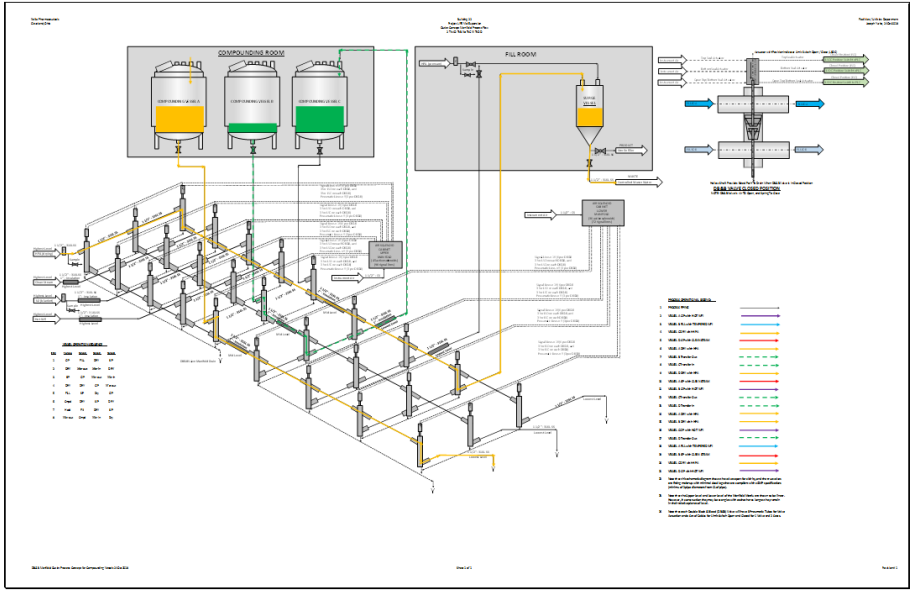
Spring Semester Internship Partnership Week 9

- **Week 9 Review / Approve Scopes of Work for Automation and Installation Bids**
  - Automation Scope of Work
  - Installation Scope of Work



Project Scope of Work

xellia PHARMACEUTICALS

Xellia Pharmaceuticals USA, LLC
Cleveland, Ohio

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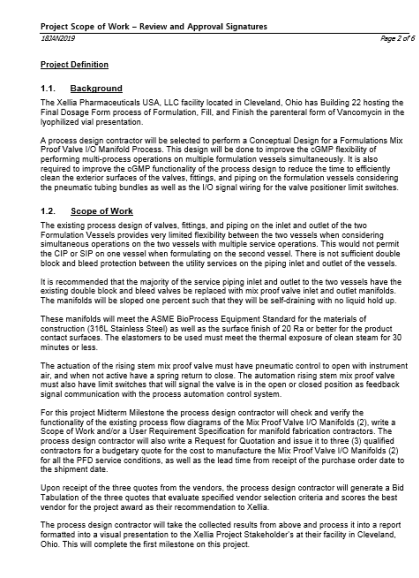

Project Scope of Work – Review and Approval Signatures
163AN2019 *Page 2 of 6*

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xellia

Spring Semester Internship Partnership Week 10

- **Week 10 Automation Request For Quotation (RFQ) and Installation RFQ: three vendors to quote (order of magnitude +/- 30%)**
  - Automation Scope of Work (need in 2 weeks)
  - Installation Scope of Work (need in 2 weeks)

Project Scope of Work

xellia PHARMACEUTICALS

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Date: 25 JAN 2019

PROCESS OWNER: Rafael Rios-Delgado, P.E., *Engineering & Maintenance Director*
Date: 25 JAN 2019

END USER: Brenda Schuler, *Compounding SME*
Date: 25 Jan 2019

PROJECT MANAGER: Joseph Yurko, P.E., *Associate Project Lead*
Date: 25JAN2019

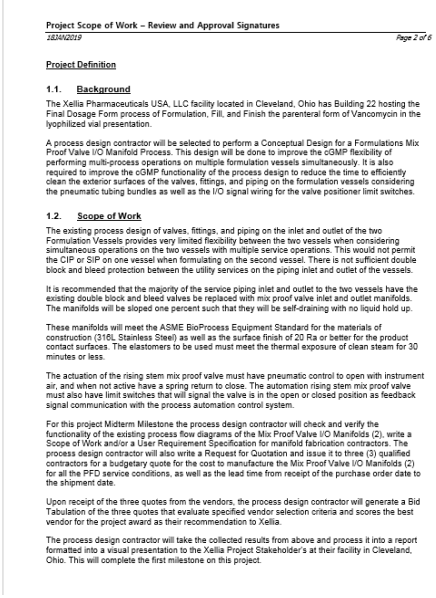
PROJECT CONSULTANTS: Steven Ellefson, *Case Consulting Ltd.*
Date:

PROJECT CONSULTANTS: Caleb Will, *Case Consulting Ltd.*
Date:

PROJECT CONSULTANTS: Brook Eagleson, *Case Consulting Ltd.*
Date:

PROJECT CONSULTANTS: Morihisa Nagai, *Case Consulting Ltd.*
Date:

Revision	Date	Revised By	Revision Summary
1	25JAN2019	Joseph Yurko	Original Document Draft.



Project Scope of Work – Review and Approval Signatures
1834N2019 Page 2 of 6

Project Definition

1.1. Background

The Xellia Pharmaceuticals USA, LLC facility located in Cleveland, Ohio has Building 22 hosting the Final Dosage Form process of Formulation, Fill, and Finish the parenteral form of Vancomycin in the lyophilized vial presentation.

A process design contractor will be selected to perform a Conceptual Design for a Formulations Mix Proof Valve I/O Manifold Process. This design will be done to improve the cGMP flexibility of performing multi-process operations on multiple formulation vessels simultaneously. It is also required to improve the cGMP functionality of the process design to reduce the time to efficiently clean the exterior surfaces of the valves, fittings, and piping on the formulation vessels considering the pneumatic tubing bundles as well as the I/O signal wiring for the valve positioner limit switches.

1.2. Scope of Work

The existing process design of valves, fittings, and piping on the inlet and outlet of the two Formulation Vessels provides very limited flexibility between the two vessels when considering simultaneous operations on the two vessels with multiple service operations. This would not permit the CIP or SIP on one vessel when formulating on the second vessel. There is not sufficient double block and bleed protection between the utility services on the piping inlet and outlet of the vessels.

It is recommended that the majority of the service piping inlet and outlet to the two vessels have the existing double block and bleed valves be replaced with mix proof valve inlet and outlet manifolds. The manifolds will be sloped one percent such that they will be self-draining with no liquid hold up.

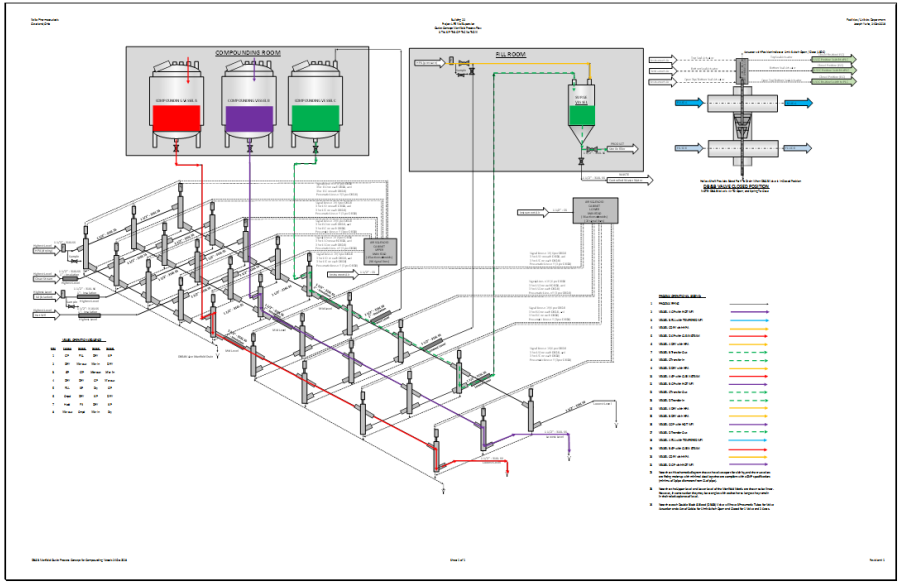
These manifolds will meet the ASME BioProcess Equipment Standard for the materials of construction (316L Stainless Steel) as well as the surface finish of 20 Ra or better for the product contact surfaces. The elastomers to be used must meet the thermal exposure of clean steam for 30 minutes or less.

The actuation of the rising stem mix proof valve must have pneumatic control to open with instrument air, and when not active have a spring return to close. The automation rising stem mix proof valve must also have limit switches that will signal the valve is in the open or closed position as feedback signal communication with the process automation control system.

For this project Midterm Milestone the process design contractor will check and verify the functionality of the existing process flow diagrams of the Mix Proof Valve I/O Manifolds (2), write a Scope of Work and/or a User Requirement Specification for manifold fabrication contractors. The process design contractor will also write a Request for Quotation and issue it to three (3) qualified contractors for a budgetary quote for the cost to manufacture the Mix Proof Valve I/O Manifolds (2) for all the PFD service conditions, as well as the lead time from receipt of the purchase order date to the shipment date.

Upon receipt of the three quotes from the vendors, the process design contractor will generate a Bid Tabulation of the three quotes that evaluate specified vendor selection criteria and scores the best vendor for the project award as their recommendation to Xellia.

The process design contractor will take the collected results from above and process it into a report formatted into a visual presentation to the Xellia Project Stakeholder's at their facility in Cleveland, Ohio. This will complete the first milestone on this project.



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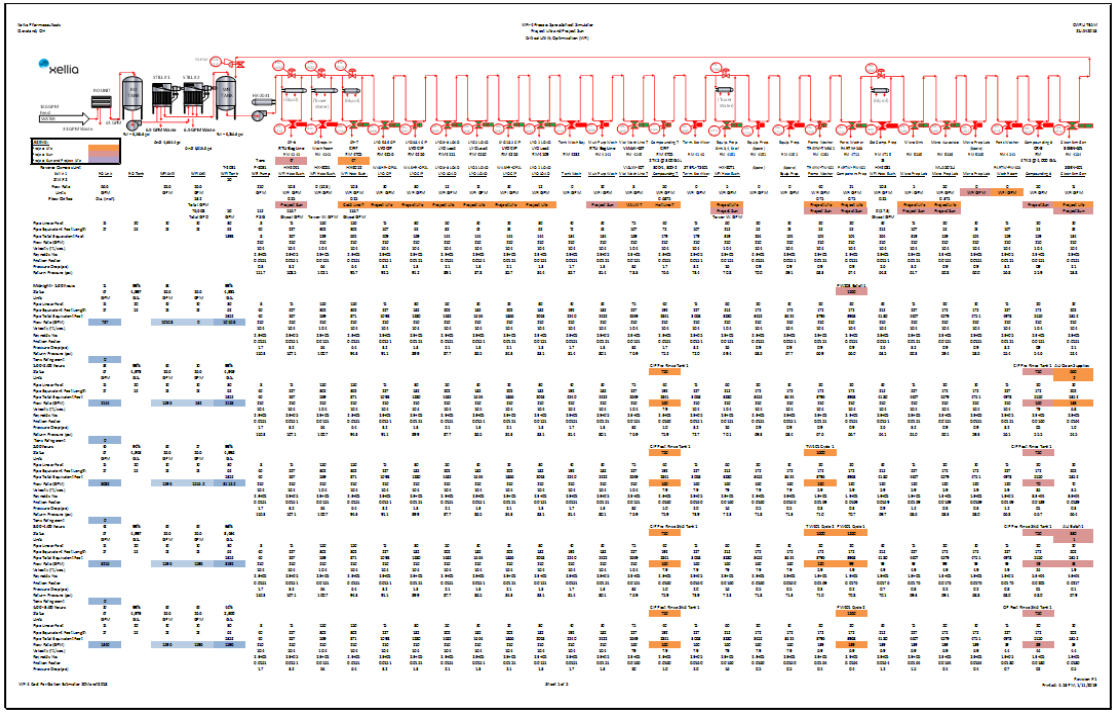
Spring Semester Internship Partnership Week 11

- **Week 11 Evaluate Formulation Process Steps on WFI Process Optimization Simulation**
  - Formulation Process Utility Service Sequence
  - WFI Process Optimization Simulation (Scale)



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Spring Semester Internship Partnership Week 12

- **Week 12 Draft final presentation with Automation & Installation vendor quote Bid Tabulation**
  - Automation Vendor Quote Bid Tabulation
  - Installation Vendor Quote Bid Tabulation

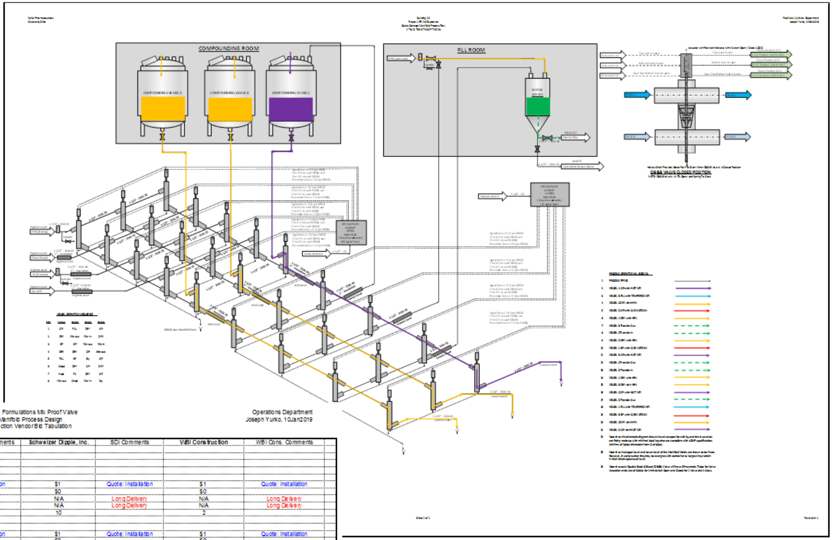
Xellia Pharmaceuticals
Cleveland, Ohio

Liquid Fill: Formulations Mix Proof Valve
I/O Manifold Process Design
Automation Vendor Bid Tabulation

Operations Department
Joseph Yurko, 10Jan2019

VENDOR CRITERIA	Engineering Est.	Rovisys	Rovisys Comments	Rockwell	Rockwell Comments	Siemens	Siemens Comments
Mix Proof Valve Man.Automation							
Inlet Mix Proof Valve Manifold							
Unit Cost	$1	$1	Quote: No Manifold	$1	Quote: No Manifold	$1	Quote: No Manifold
Added Cost (tax, S&H)	$0	$0		$0		$0	
Code Description Delivery ARO	N/A	N/A	Delivery Time Not Quoted	N/A	Delivery Time Not Quoted	N/A	Delivery Time Not Quoted
Code Programming Delivery ARAD	N/A	N/A	Delivery Time Not Quoted	N/A	Delivery Time Not Quoted	N/A	Delivery Time Not Quoted
Score	19	19		10		2	
Outlet Mix Proof Valve Manifold							
Unit Cost	$1	$1	Quote: No Manifold	$1	Quote: No Manifold	$1	Quote: No Manifold
Added Cost (tax, S&H)	$0	$0		$0		$0	
Code Description Delivery ARO	N/A	N/A	Delivery Time Not Quoted	N/A	Delivery Time Not Quoted	N/A	Delivery Time Not Quoted
Code Programming Delivery ARAD	N/A	N/A	Delivery Time Not Quoted	N/A	Delivery Time Not Quoted	N/A	Delivery Time Not Quoted
Score	19	19		10		2	
Inlet Manifold Automation							
Unit Cost	$32,400	$1	Quote: Prog. & Cabinets	$1	Quote: Prog. & Cabinets	$1	Quote: Prog. & Cabinets
Added Cost (tax, S&H)	$6,480	$0		$0		$0	
Code Description Delivery ARO	1 to 2 Weeks	N/A	Long Delivery	2 to 3 Weeks	Long Delivery	3 to 4 Weeks	Long Delivery
Code Programming Delivery ARAD	15 to 16 Weeks	N/A	Long Delivery	22 to 24 Weeks	Long Delivery	TBD at time of order Weeks	Long Delivery
Score	2	2		2		2	
Outlet Manifold Automation							
Unit Cost	$32,400	$1	Quote: Prog. & Cabinets	$1	Quote: Prog. & Cabinets	$1	Quote: Prog. & Cabinets
Added Cost (tax, S&H)	$6,480	$0		$0		$0	
Code Description Delivery ARO	1 to 2 Weeks	N/A	Long Delivery	2 to 3 Weeks	Long Delivery	3 to 4 Weeks	Long Delivery
Code Programming Delivery ARAD	8 to 9 Weeks	N/A	Long Delivery	22 to 24 Weeks	Long Delivery	TBD at time of order Weeks	Long Delivery
Score	2	2		2		2	
Total Cost	8	8		8		8	
Total Score							
	$77,762	**$5**	Minimum Cost	**$5**	Average Cost	**$5**	Maximum Cost
% Difference (Basis: Lowest Quote)	**50**	**50**		**32**		**16**	
	N/A	99.99%		99.99%		99.99%	
		Best Quote		Mid Quote		Worst Quote	
VENDOR CRITERIA						**SCORING CRITERIA (points: best, medium, worst)**	
1. Only bid 3 relatively same-sized contractors.							
2. Pre-bid meeting request for a legitimate bid.						10, 5, 1	Cost relative to Engr. Est.
3. Deal with the exceptions to put the quotations on the same plane.							
4. Generate your own independent estimate.						9, 5, 1	Delivery with Customs Time
5. Order the quotes from lowest to highest and place your estimate in this ranking.							
6. If the design house estimate does not fall within the spread, discuss it with them.						8, 0, 0	Xellia Qualified & Bonded
7. Meet with each contractor to go over the scope one more time, to compare their estimates to yours, and to negotiate the price if required.							
8. Award the job to whom you can best justify doing so.						7, 4, 1	Xellia experience with vendor
9. Reference Vessel Data Sheets for design detail specifications (issued to all vendors for quotation basis)							
						6, 3, 1	Vendor reputation (D&B)
LEGEND:							
Red Lettering or shaded cell denotes concern						Sum Total for three quotes	Quote totals rank's score
AR Value = $250,000 to $300,000							Recommend Highest Score
						https://www.dnb.com/products/	Verify Dunn & Bradstreet Ranking

Mix Proof Valve Manifold Vendor Bid Tab Rev 1 — Sheet 1 of 1 — Revision # 1, Printed: 4:12 PM, 1/22/2019



Xellia Pharmaceuticals
Cleveland, Ohio

Liquid Fill: Formulations Mix Proof Valve
I/O Manifold Process Design
Construction Vendor Bid Tabulation

Operations Department
Joseph Yurko, 10Jan2019

VENDOR CRITERIA	Engineering Est.	Harner Plumbing	Harner Plum. Comments	Schweizer Dipple, Inc.	SDI Comments	WBI Construction	WBI Cons. Comments
Mix Proof Valve Man. Installation							
Inlet Mix Proof Valve Manifold							
Unit Cost	$13,500	$1	Quote: Installation	$1	Quote: Installation	$1	Quote: Installation
Added Cost (tax, rigging)	$2,700	$0		$0		$0	
Drawing Delivery ARO	1 to 2 Weeks	N/A	Long Delivery	N/A	Long Delivery	N/A	Long Delivery
Manifold Delivery Installation	15 to 16 Weeks	N/A	Long Delivery	N/A	Long Delivery	N/A	Long Delivery
Score	19	19		10		2	
Outlet Mix Proof Valve Manifold							
Unit Cost	$13,500	$1	Quote: Installation	$1	Quote: Installation	$1	Quote: Installation
Added Cost (tax, rigging)	$2,700	$0		$0		$0	
Drawing Delivery ARO	1 to 2 Weeks	N/A	Long Delivery	N/A	Long Delivery	N/A	Long Delivery
Manifold Delivery Installation	15 to 16 Weeks	N/A	Long Delivery	N/A	Long Delivery	N/A	Long Delivery
Score	19	19		10		2	
Inlet Manifold Automation Cabinets							
Unit Cost	$13,500	$1	Quote: Installation	$1	Quote: Installation	$1	Quote: Installation
Added Cost (tax, rigging)	$2,700	$0		$0		$0	
Drawing Delivery ARO	1 to 2 Weeks	N/A	Long Delivery		Long Delivery		Long Delivery
Cabinet Delivery Installation	15 to 16 Weeks	N/A	Long Delivery		Long Delivery		Long Delivery
Score	2	2		2		2	
Outlet Manifold Automation Cabinets							
Unit Cost	$13,500	$1	Quote: Installation	$1	Quote: Installation	$1	Quote: Installation
Added Cost (tax, rigging)	$2,700	$0		$0		$0	
Drawing Delivery ARO	1 to 2 Weeks	N/A	Long Delivery		Long Delivery		Long Delivery
Cabinet Delivery Installation	8 to 9 Weeks	N/A	Long Delivery		Long Delivery		Long Delivery
Score	2	2		2		2	
Total Cost	8	8		8		8	
Total Score							
	$64,800	**$5**	Minimum Cost	**$5**	Average Cost	**$5**	Maximum Cost
% Difference (Basis: Lowest Quote)	**50**	**50**		**32**		**16**	
	N/A	99.99%		99.99%		99.99%	
		Best Quote		Mid Quote		Worst Quote	
VENDOR CRITERIA						**SCORING CRITERIA (points: best, medium, worst)**	
1. Only bid 3 relatively same-sized contractors.							
2. Pre-bid meeting request for a legitimate bid.						10, 5, 1	Cost relative to Engr. Est.
3. Deal with the exceptions to put the quotations on the same plane.							
4. Generate your own independent estimate.						9, 5, 1	Delivery with Customs Time
5. Order the quotes from lowest to highest and place your estimate in this ranking.							
6. If the design house estimate does not fall within the spread, discuss it with them.						8, 0, 0	Xellia Qualified & Bonded
7. Meet with each contractor to go over the scope one more time, to compare their estimates to yours, and to negotiate the price if required.							
8. Award the job to whom you can best justify doing so.						7, 4, 1	Xellia experience with vendor
9. Reference Vessel Data Sheets for design detail specifications (issued to all vendors for quotation basis)							
						6, 3, 1	Vendor reputation (D&B)
LEGEND:							
Red Lettering or shaded cell denotes concern						Sum Total for three quotes	Quote totals rank's score
AR Value = $250,000 to $300,000							Recommend Highest Score
						https://www.dnb.com/products/	Verify Dunn & Bradstreet Raging

Mix Proof Valve Manifold Vendor Bid Tab Rev 1 — Sheet 1 of 1 — Revision # 1, Printed: 4:13 PM, 1/22/2019

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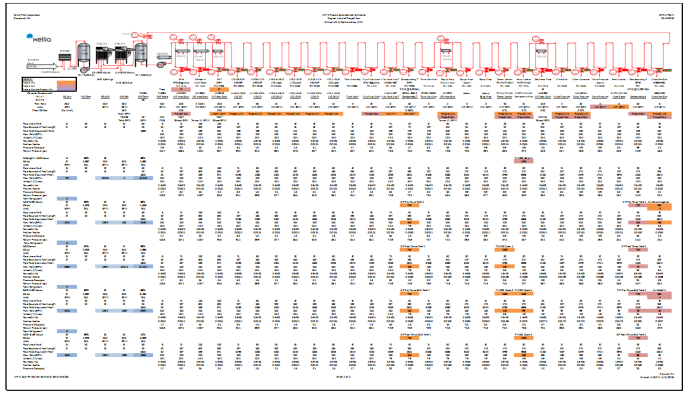
Spring Semester Internship Partnership Week 13

- **Week 13 Final Presentation, Turn Over Package & Lessons Learned**
  - Final Presentation
    - WFI Simulation Optimization for 2 Fill Line Demands & Costs
    - CS Simulation Optimization for 2 Fill Line Demands & Costs
    - HPA Simulation Optimization for 2 Fill Line Demands & Costs
    - Liquid N2 Simulation Optimization for 2 Fill Line Demands & Costs
  - Turn Over Package
    - Simulation Spreadsheets for WFI, CS, HPA and N2 Systems
    - MS PowerPoint Presentations for Midterm, Poster, and Final
  - Lessons Learned
    - Project was well done considering time and difficulty factors
    - Recommendations to improve document version labeling
    - Project Management approach worked very well (not part of classes)



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Win-Win With University Partnerships and Your Society

SUMMARY PARTNERSHIP APPROACH TEMPLATE
(for society / company contact)

- **Engage local universities to participate in partnership**
  - Discipline of Engineering (i.e, AIChE, ASME, IEEE, ISA…etc.)
  - Contact Student Chapter Advisor at local university (CSU, CWRU…UA)
- **Propose a program of interest between company and university**
  - Lunch & Learn: Develop 40 min. presentations on 12 weekly topics
  - Internship: Develop a series of weekly input/output steps for students
- **Provide a schedule of milestones to be accomplished**
  - Lunch & Learn: Create a midterm and final open group exam
  - Internship: schedule what deliverables are due and when
- **Set the expectations for the final product to be delivered**
  - Lunch & Learn: attend and participate in presentations and exams
  - Internship: Turn over of project files after project presentation is made

Win-Win With University Partnerships and Your Society

Q & A

Continuing Professional Development Certificate

xellia PHARMACEUTICALS

The Cleveland, Ohio Manufacturing Facility of

Xellia Pharmaceuticals USA, INC.

Is pleased to recognize and present

Nandini Padaraju

with 12.0 hours of CPD

Good Design Practices for GMP Pharmaceutical Facilities

As presented by Joseph Yurko, P.E., John Mylar, P.E., Daniel Heinrich, Stephanie McClure, John Juchnowski, Kruttika Patel, and Noura Awad during the Lunch & Learn Seminars in conjunction with the Student Chapter of AIChE at the Washkewicz College of Engineering

Cleveland State University

this 6th day of December, 2018

Joseph Yurko, P.E. — Associate Project Lead

Sandra Torres — Site General Manager

Rafael Rios-Delgado — Engineering & Maintenance Director

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CLEVELAND STATE UNIVERSITY

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GET ADMISSION INFO

GIVE TO CSU

Improving workforce skills for pharmaceutical and life science industries

A key issue facing pharmaceutical manufacturers operating in the United States is the need for highly skilled chemical engineers who are well versed in regulatory requirements mandated by federal agencies including the Food and Drug Administration. Unfortunately, many chemical engineering degree programs do not feature a comprehensive regulatory curricula that matches to current industry need.

To address this, Cleveland State University has partnered with **Xellia Pharmaceuticals** to create a **Current Good Manufacturing Practices (CGMP) design certification program** that provides future workers with the skills necessary to meet workforce demand.

"Xellia recently opened a manufacturing facility in Bedford, Ohio and has been actively recruiting engineers to assist with production ramp-up," notes **Niels Lynge Agerbaek**, General Manager for Xellia Cleveland. "We realized that there was a lack of workforce understanding of the regulatory requirements that are essential to drug manufacturing. We did not have the ability to create a full service training program on our own so looked to partner with an institution to enhance the educational programming that already existed."

"CSU continually investigates opportunities to improve our degree programs to better meet the needs of industry, and this opportunity was a chance to provide additional skills that will make our graduates more valuable to Xellia and numerous other pharmaceutical manufacturers," says **Joanne Belovich**, chair of the Department of Chemical and Biomedical Engineering at CSU.

Xellia Pharmaceuticals developed a seven-week course that offered instruction in a host of regulatory topics, including architectural design, high purity water systems and sterile manufacturing, while also providing tours of current manufacturing operations and an opportunity to interact with engineers working in the field.

Xellia's engineers and managers taught the course and Belovich worked with the student chapter of the **American Institute of Chemical Engineers** and department staff to recruit participants and organize the events. Over 60 students completed the spring edition of the course and received certification. CSU and Xellia Pharmaceuticals plan to offer it again next year and hope to open it up to additional majors on campus.

"This partnership allowed our company to address a specific workforce need and identify talented students for future employment opportunities," says **Joseph Yurko**, a CSU chemical engineering alum who serves as an associate project lead at Xellia. "It also assisted CSU in providing additional professional training and development for their students that will make them more employable in multiple facets of the pharmaceutical industry. It truly is a win-win."

2018 Capstone Internship Certificate

xellia PHARMACEUTICALS

The Cleveland, Ohio Manufacturing Facility of

Xellia Pharmaceuticals USA, INC.

Is pleased to recognize and present

Cristina DiFranco

For the 2018 Spring Semester Internship of the Senior Class Aquality Team performing

Process Simulation and Optimization of Clean Utility Systems

supervised by Joseph Yurko, P.E.

in conjunction with

AIChE and the Department of Chemical and Biomolecular Engineering at

Case Western Reserve University School of Engineering

this 25th day of April, 2018

Joseph Yurko, P.E. — Associate Project Lead

Kenneth Ruggiero — Head of Facilities

Robert Sanchez — Head of Human Resources

Michael Chojnacki — Clean Utilities Manager

xellia