ADAM LADINE

BIOMEDICAL ENGINEER

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EDUCATION

University of Massachusetts Lowell, Lowell, MA
M.S. Biomedical Engineering and Biotechnology (3.5)

January 2016 - May 2018

- Coursework included laboratory experience with cell culture and harvesting, clarification, ultrafiltration, protein assays, spectrophotometry, Western Blot, and polymerase chain reaction (PCR) in the production of Taq DNA polymerase from E. coli

University of Oklahoma, Norman, OK
B.S. Chemical Engineering (3.6)

September 2009 - May 2013

- Laboratory experience with unit operations, including distillation, ion exchange chromatography, packed column mass transfer, membrane separations, and heat exchangers

EXPERIENCE

SHIRE PHARMACEUTICALS, Lexington, MA - *Process Engineering Co-op*

January 2017 - July 2017

- Supported both daily and long term cGMP manufacturing operations and projects for mammalian cell culture production lines, with focus on upstream single-use bioprocessing
- Drove an improvement change to a GMP quality documentation system for single-use component management
- Developed engineering drawings for single-use component management for two capital projects
- Assisted in troubleshooting and deviation investigations

WATER ENGINEERING, Mead, NE — *Chemical Service Engineer*

June 2013 - November 2014

- Managed chemical systems for 60 clients in midwest
- Provided monthly on-site service and field testing, including conductivity, pH, and chemical tests
- Developed client-specific chemical treatment programs
- Restored 23 severely neglected or mismanaged systems
- Performed laboratory testing of corrosion coupon samples
- Managed reagent inventory

SKILLS

Programming
Python, Visual Basic, Matlab, R, SQL, HTML, JavaScript

Software
Bluebeam Revu, Process Historian, MS Office, Linux

CAD Software
SolidWorks, Fusion360, Aspen Hysis

Languages
American Sign Language, Spanish

Laboratory
Chromatography, Polymerase Chain Reaction (PCR), Electrophoresis, Spectrophotometry

Engineering
FMEA, FEA

CERTIFICATIONS

FE/EIT (MA #24848)
Python PCAP (in progress)

AWARDS

National Merit Scholar
Eagle Scout

PROFESSIONAL MEMBERSHIP

International Society of Pharmaceutical Engineers

Portfolio Work

Adam LaDine

The following articles are also available at https://adam.ladine.me/portfolio

Data-based Troubleshooting

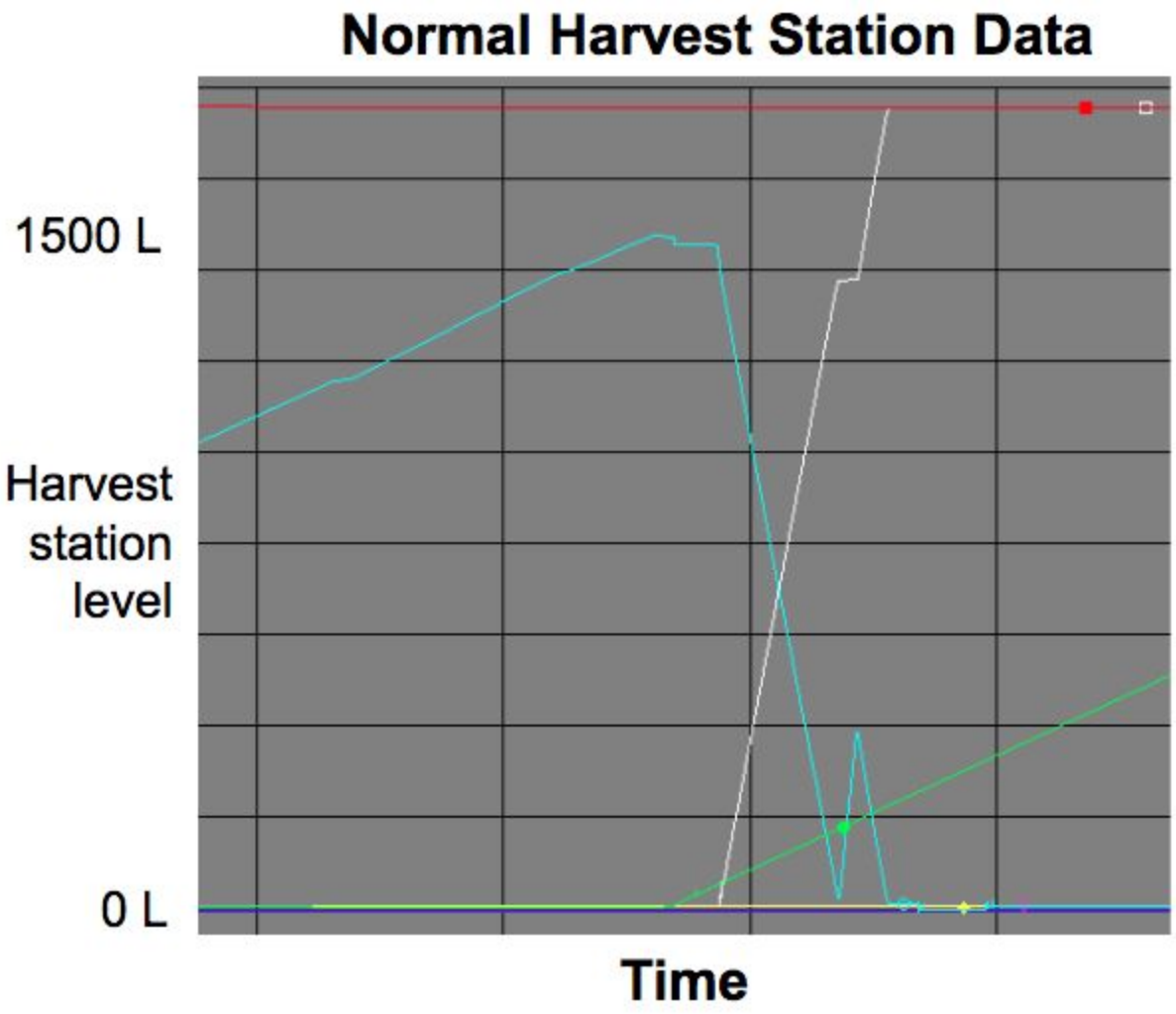
This is a brief case study in my use of data from the manufacturing floor to assist in the troubleshooting of a manufacturing process.

For context, this occured during an engineering run for a tech transfer project. This engineering run is not intended to result in the production of sellable drug product.

This incident takes place about 3-4 weeks into the engineering campaign. The production bioreactor typically runs for about a month, depending on cell viability towards the end of the campaign. Every day, perfusion through the bioreactor produces approximately 1500 L of raw harvest, which is collected in a fresh vessel each day. This contains the unpurified, unfiltered, raw drug product. It also contains cell debris, cellular waste, nutrients, and lots and lots of water.

The first step in refining the raw drug product is clarification: passing raw harvest through racks of filtration pods to remove cell debris and other large contaminants. The clarified harvest is returned to another collection vessel.

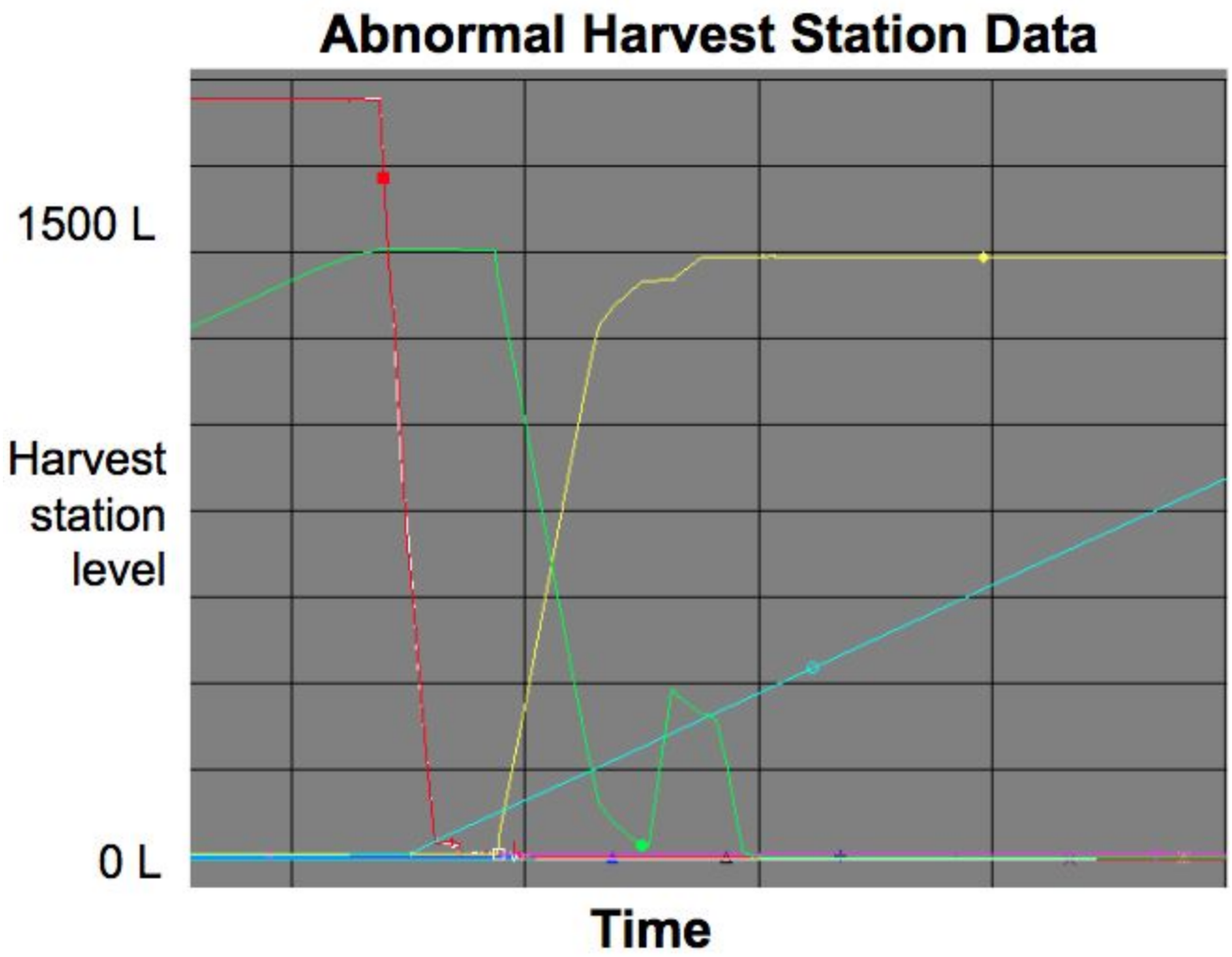
The liquid levels within the collection vessels are monitored using weight as a proxy for level, asserting that the density is as water (1 kg = 1 L). For a normal clarification procedure, the levels within the collection vessel look like this:



Each vessel is represented by a different color line. We can see Blue approach its 1500 L maximum level. Flow to it is cut off, and the bioreactor output is redirected to Green, which begins rising. The Blue container's raw harvest is pumped through clarification filters and collected in the White container. Then, a chase buffer is added to Blue and pumped through the filter as well, to collect any residual drug product. Later, White and Red (already clarified from the day prior) will be pooled together for further downstream processing.

During one such clarification procedure, manufacturing reported that the peristaltic pumps driving the clarification process were turning themselves off unexpectedly. This issue was escalated to Process Engineering for investigation.

The data for the troubled clarification procedure looked quite different:



The Green container has filled, and bioreactor production is rerouted to Blue. (At the same time, Red and White are sent elsewhere for further downstream purification, but that is not part of this problem.) Then, Green is pumped through clarification filters to Yellow.

If the problem was merely that the peristaltic pumps were turning off, we would expect to see Green and Yellow abruptly go flat as the levels within stop changing. But that's not what the data shows. Instead, we see the flow rate from Green to Yellow decreasing as the first stage of clarification nears completion. Then, the chase buffer is added to Green, and very little of the chase buffer is successfully pumped through before the pumps turn off. Eventually, remaining chase buffer in Green is dumped to Process Drain.

The slow decrease of flow rate suggests that the root problem did not lie with the pumps, but rather with the filters: as mass accumulates in a filter, flow is impeded and ΔP must increase. A look at the pressure data (not shown) corroborated this answer: as the flow rate slowed, the pressure drop across the filter was increasing as it retained mass.

During a month-long production campaign, the viability and integrity of the cells in the production bioreactor are expected to decrease over time: each cell is centrifuged once daily on average, and these mechanical forces can damage or kill the cells. Mechanical forces from the agitator and the sparge gas bubbles can also damage cells. Therefore, the amount of cell debris in the raw harvest increases with time.

Knowing this, the answer presented itself: the cells had deteriorated faster than initially anticipated, and clogged the clarification filters ahead of schedule. As the filters clogged, the filter inlet (pump outlet) pressure increased. When the pump outlet pressure reached its hi-alarm threshold, the pump automatically turned off for safety reasons.

I communicated this information to Process Development. By adding more filters in parallel for subsequent clarification procedures, this problem was avoided for the remainder of the engineering campaign.

DCFD Drawing Improvements

This is an overview of a new drawing style that I developed for the management of single-use parts in process engineering.

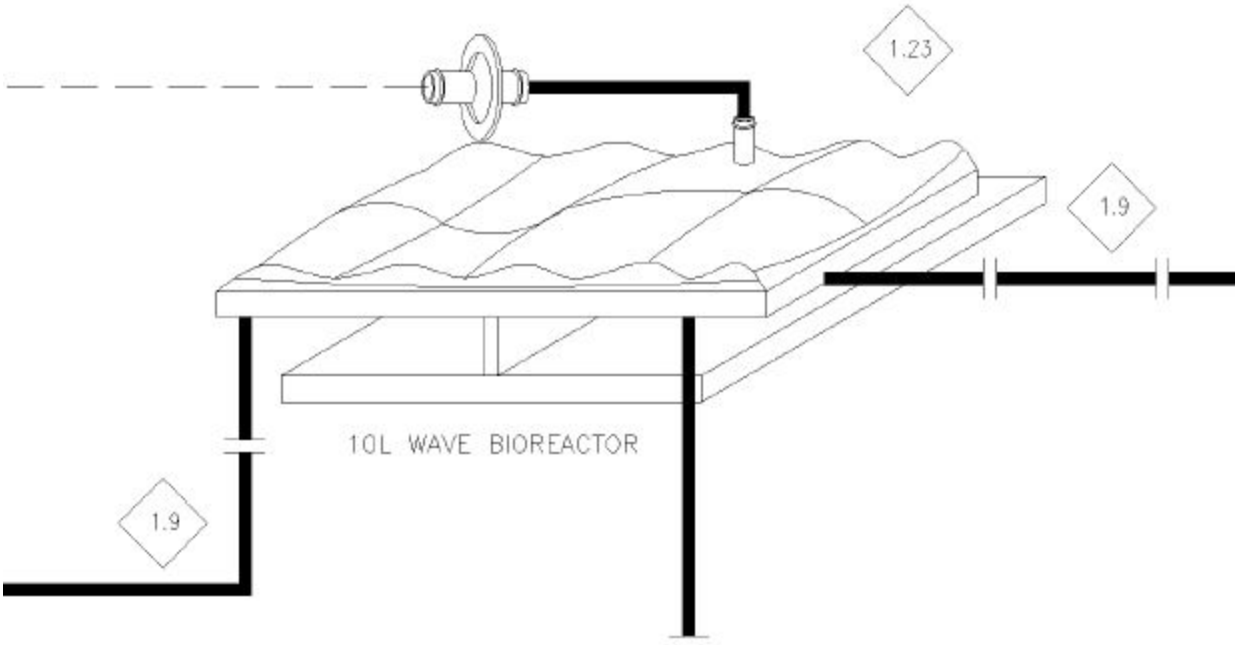
Shire Pharmaceuticals in Lexington, Massachusetts makes heavy use of single-use technology in their manufacturing operations. To manage single-use parts, they use Disposable Component Flow Diagrams (DCFDs), a type of Process Flow Diagram that specifically identifies where single-use parts are located in the process equipment.

DCFDs are created per process step, not per equipment. If redundant equipment is present, the DCFD applies to any of the redundant options that are validated for use in that process step.

During my time at Shire, I was able to develop an improvement to Shire's DCFDs that was ultimately codified in their SOPs.

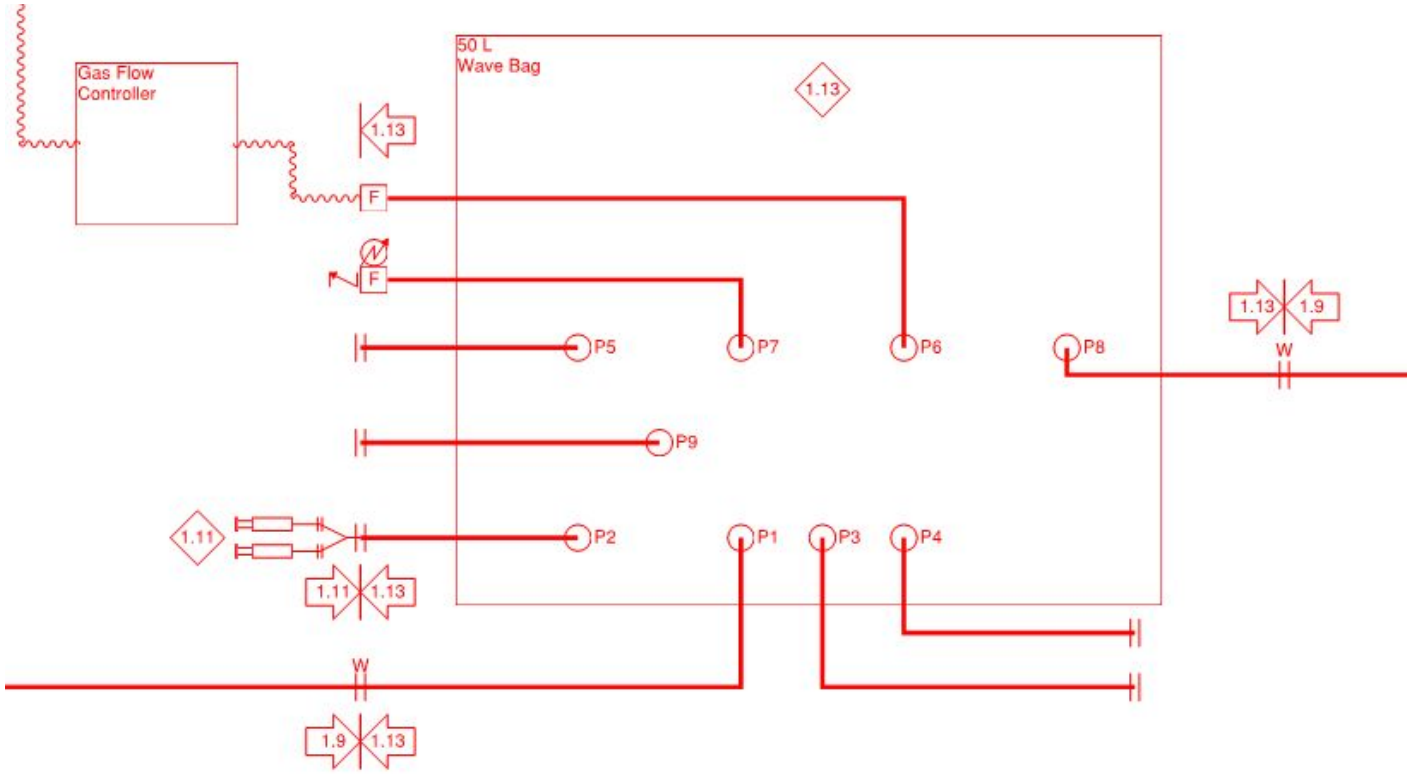
In a DCFD, single-use parts are identified by a number in a diamond. The drawing is accompanied by a table of parts, organized by "diamond number", listing out all single-use parts approved for that point in the process.

Here is a DCFD drawing snippet of a wave bioreactor, used in upstream cell culture:



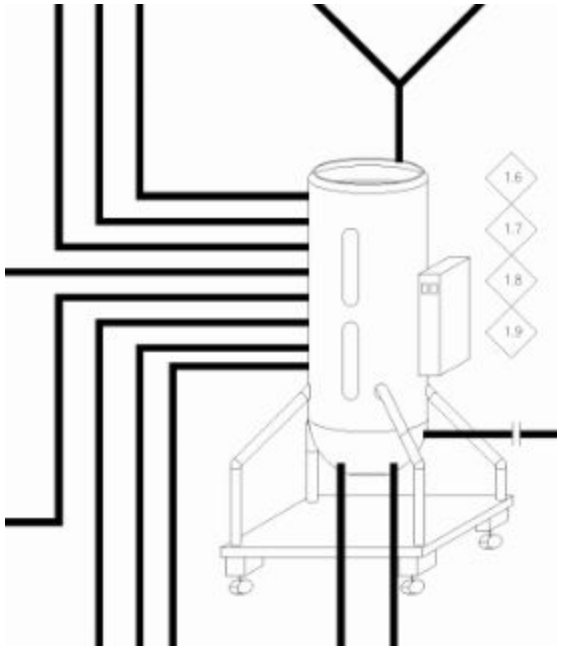
To find the parts approved for use as a 10L wave bag bioreactor, the reader would look up part 1.23 in the corresponding table. Similarly, to find the tubing used at the inlet and outlet of the wave bag, the reader would look up part 1.9.

This is my redrawing of a similar part:



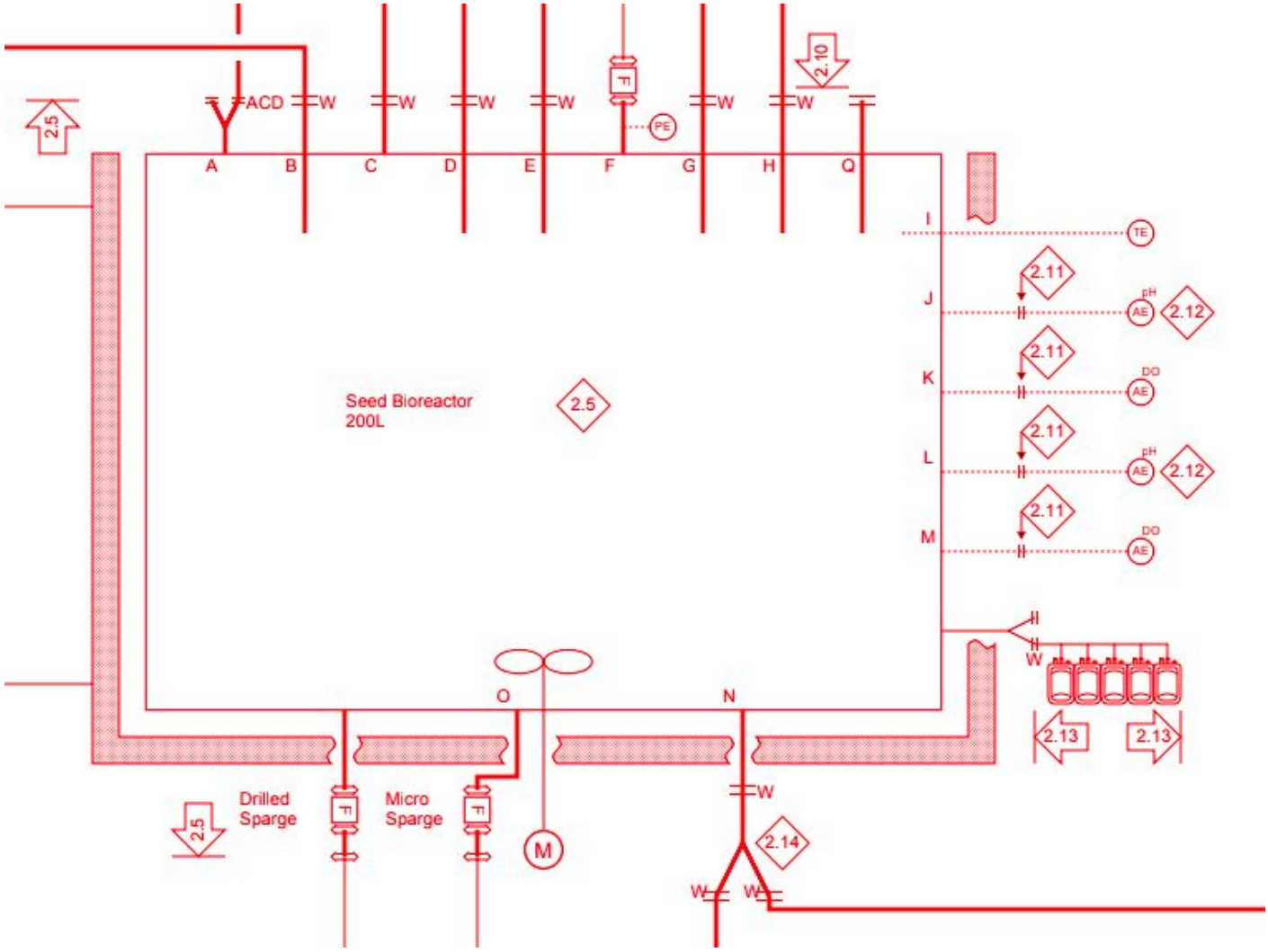
Note the use of block arrows to indicate boundaries between parts. Since bioreactor bag 1.13 includes tubing stems, the block arrows clearly indicate that tubing 1.9 does not extend all the way to the bag itself. Additionally, the ports on the wave bag are placed in their actual position.

This was the standard symbol for an upright tank bioreactor, used regardless of what the bioreactor actually looked like:



In this snippet, it is not clear which parts are intended to be identified by the diamonds 1.6, 1.7, 1.8, and 1.9.

Furthermore, the lines that are drawn connecting in the back actually connect on top, and the one line coming out the top actually goes on the bottom.



As with my redrawn wave bag, my redrawn upright bioreactor shows the connections drawn in a way that reflects the real-world configuration of the equipment. Functions of tagged parts are immediately apparent without having to consult the parts table. I even included some P&ID notation for the disposable sensors to improve readability.

These stylistic and symbolism changes were positively received by the relevant SMEs. They recognized the value and time efficiency generated by the cleaner and more informative drawing style, and an SOP change was approved to allow for my new style of DCFD.

Upon contacting a former colleague about 10 months after leaving Shire, I was told that others have begun using my style of drawing in their own work.