

DSM





DSM Presentation

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History of Site

- **Incorporated in 1976 (Wyckoff Chemical Co.)**
 - Dr. Wyckoff a Chemist who didn't know much about business started the company. A sales guy with a Masters in chemistry helped the company become fluid.
- **Site is 47 acres with 20 acres in use**
- **We have approximately 150 fulltime employees**
- **Company was acquired by Catalytica Inc in 1999**
 - Their intentions were to sell us for a higher price.
- **Catalytica was acquired by DSM in 2000**
 - Paid too much for the company.
- **Part of DSM Pharma Chemicals which is in Life Science Cluster along with sister sites at Venlo (Netherlands) and Linz (Austria)**



What we do

- **Develop and manufacture drug intermediates and API's (active pharmaceutical ingredients) to the generic Pharmaceutical Industry. Also manufacture non-pharmaceutical materials under cGMP conditions.**
- **Does anyone know what an API is?**
- **Produce over 40 different products.**
- **Support 6 API's or API intermediates that are in Clinical Phase II/III.**
- **Does anyone know what a clinical trial is?**



cGMP Manufacturing

All Processes & Equipment operate under Current Good Manufacturing Processing, cGMP. ICH guidelines, Q7a.

- Documented and historized process records (recipes).
- Record history of equipment usage and it's cleaning.
- Record any deviations (planned or not planned), which include reworks or disposal of product.

Documentation is to keep track in case a medication has an issue. Authorities are able to trace the lot all the way back to the original maker along with the raw materials used to make that product.



Product Applications

Produce API's or API Intermediates for a broad range of therapeutic areas including:

Anti-inflammatory

Anti-fungal

Cardiotonic

Cancer Treatment

Anti-psychotic

Antibiotics

AIDS Treatment

Blonde color dye

Elastic centers of golf balls



Process Capabilities

We produce an array of compounds with varied chemical structures requiring organic synthetic routings:

Enzymatic Resolution (Chiral Specific)

Homogeneous Catalysis (Pd w/ ligands)

Heterogeneous Catalysis (Pd/C)

Esterifications, Alkylations, Grignards

(Heck, Suzuki, Buchwald Amination)

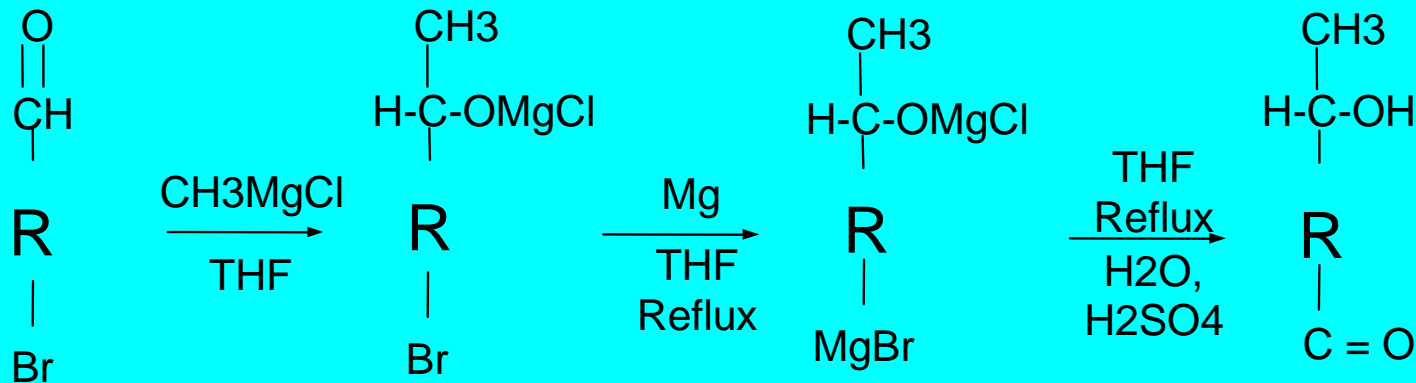
Low & Med. Pressure Hydrogenation (20-500 psig)

Na+Borohydride reductions

Thin Film Distillation



Aromatic Grignard



- Reactions are extremely sensitive to water and air and are VERY EXOTHERMIC, the heat load is sizable and requires cooling.
- Special instructions for this type of reaction.
 - Raws are charged in portions to ensure reaction starts. Lab tests the batch for reaction completion.
 - Reaction can not be started unless an Operator is present throughout reaction.

Avg. Product Life is 6 yrs

Since the average product life is 6 years at our facility we need to keep bringing in new products.

Of those new products only 1 of approx. 6 make it to become a stable product.

Work with virtual companies and regular pharma in small scale manufacturing to keep bringing in new products.

Because of the high turn over there is emphasis on scale up and change over at our company.

Due to the expediency of product to market we do not fully characterize our processes when they hit the production floor.

OPPORTUNITY!

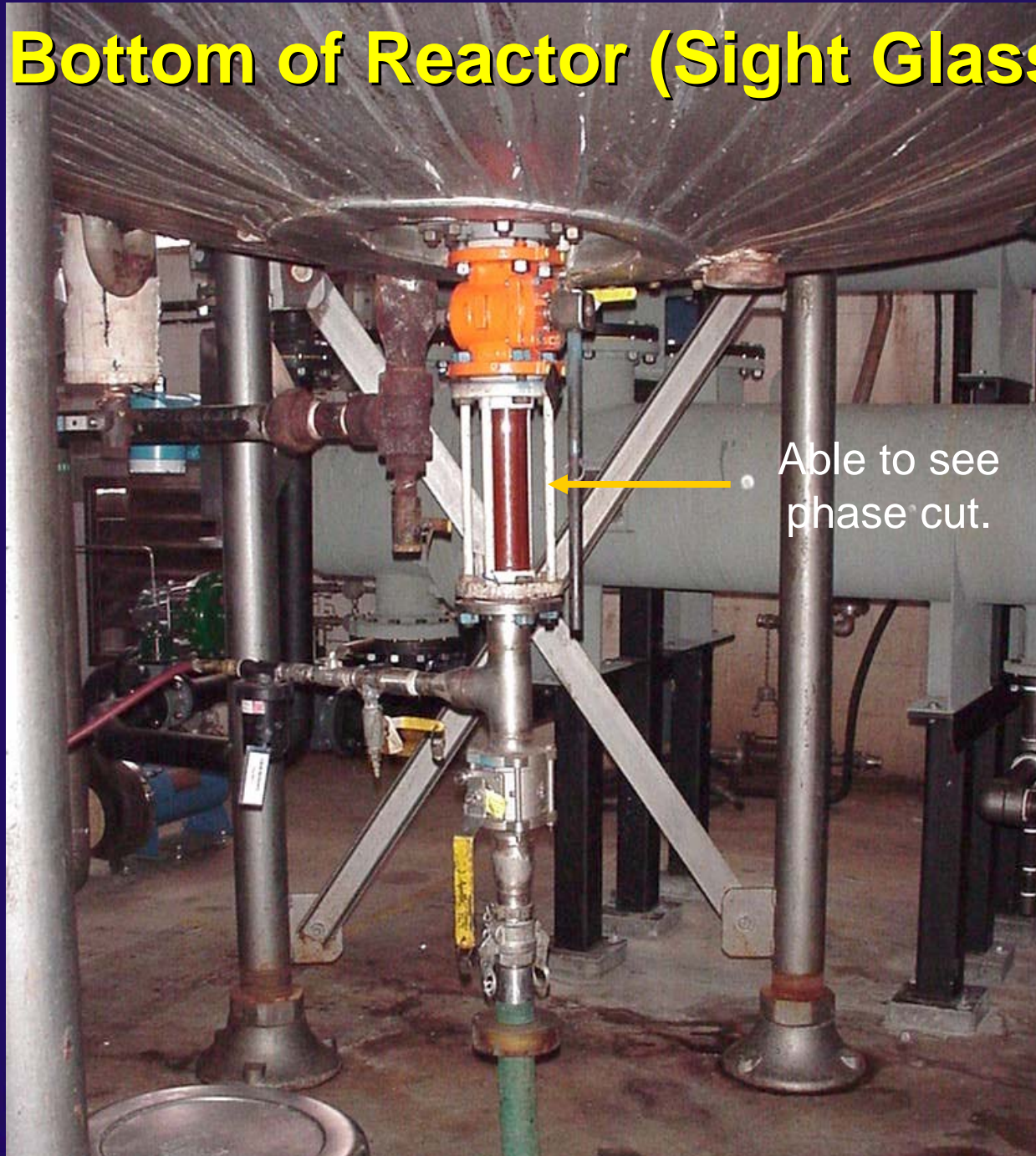


Some of Our Scale Up Issues

- Agitation – Tip speed of agitators increases.
- Heat transfer – Is lowered due to our vessel configuration.
- Phase cuts – I.e. Water and Toluene cut is more precise on larger scale.



Bottom of Reactor (Sight Glass)



Able to see
phase cut.

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General Reactor Information

- **60,000+ gallons of reactor capacity.**
 - 50 – 500 gal (SMU)
 - 1k – 4k gal full scale.
- **Built in three Sections**
 - 1978 “East Plant” – 16,000 gallons
 - 1988 “West Plant” – 30,000 gallons
 - 1999 “Plant 2” – 16,000 gallons
- **Temperature Range: -20 °C to 150 °C (LTC – Steam)**
- **Approx. 70% of equipment is glass; the rest is stainless steel with some Hastelloy.**



Inside a Glass Reactor



Support Equipment

- 4 Heinkel Centrifuges – One Hastelloy
- 2 Top Loading Centrifuges
- Thin-Film Evaporator
- Hydrogenators (25-500 psig)
- 2 Double Cone Tumble Dryers
- Vacuum Tray Dryer or Small Tumble Dryer for low volume products



Auto Un-loading Centrifuge



Centrifuge Drum Transition



Site Introduction



Unlimited. **IBM**

Thin Film

Distillate

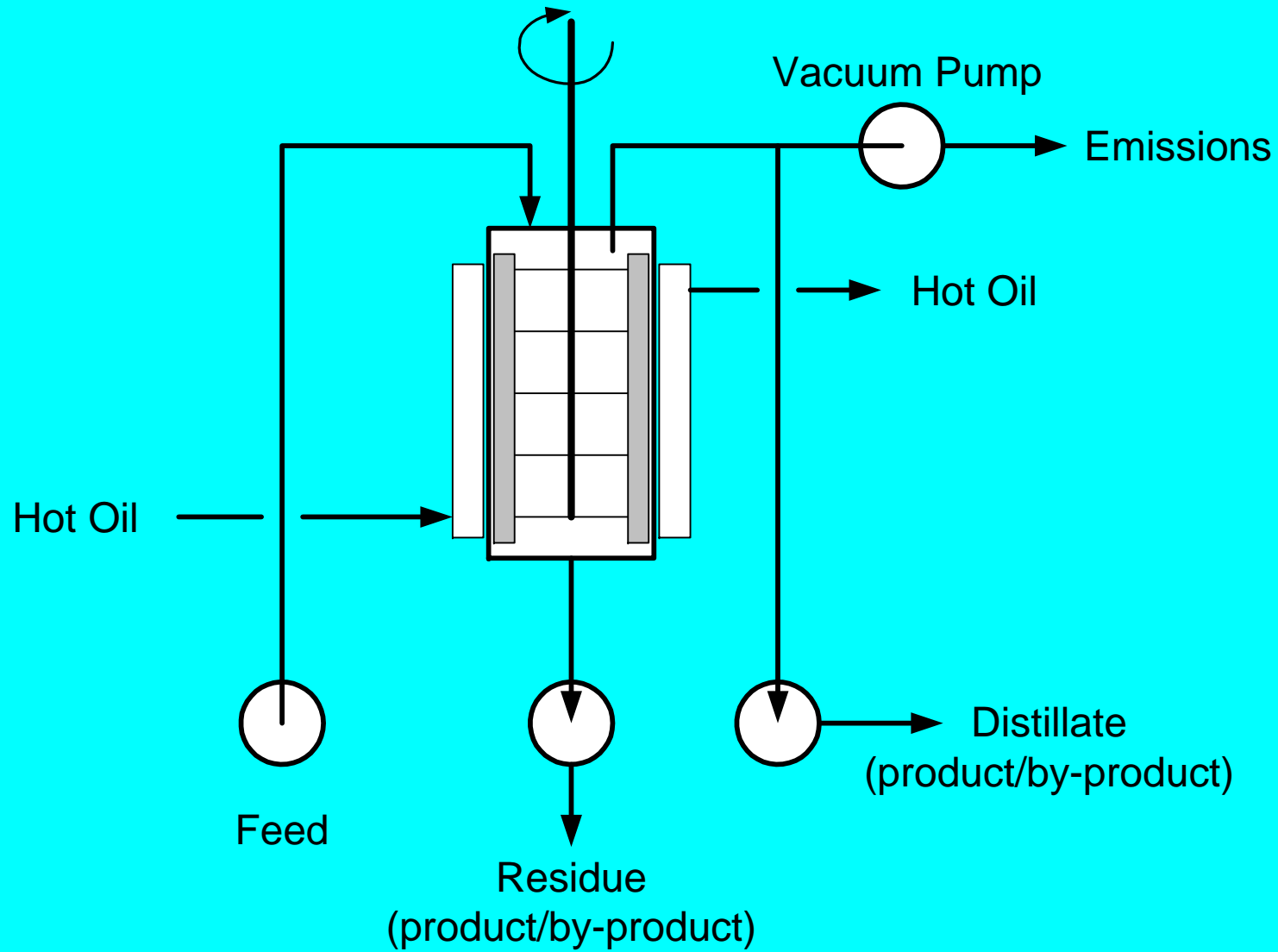
Residue

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ted. **DSM**



Wiped Thinfilm Evaporator



Double Cone Dryer



Has vacuum and cooling/
heating while rotating.

cGMP Kilo Lab

- Two 25 Liter Glass Vessels
- Aurora Filter for Isolation and Drying
- - 40 °C to 200 °C Range
- Kilo Lab operated under cGMP conditions



Preparing Drums



Warehouse



Successful Career

- Understanding the chemistry and physical characteristics of the process will greatly help your success at any company.
- Some of the greatest cost reductions happen on the Plant floor. I.e. Chemistry and Equipment
- DATA, DATA, DATA
- Always try to back up your findings with data when acquiring capital for equipment and improvements. The information may show that the improvement is not cost effective.



Situation I w/o Data

Product was off-color, pink

We attributed the color issue to glass damage on vessel and metal being exposed thus dissolving iron into the system. Testing showed that iron was complexed to product.

Vessel and equipment were not damaged!

We then said that it was probably a dirty hose or raw material. This was a 1 week investigation.

A deviation in the record said that the load cells on the HCl tank was not working. This gave false weight readings.

It was mentioned that we could have charged too much HCl to batch, HCl has small amts of free iron.

pH of product can go to 0.0 without a problem, adding more HCl should not be a problem.

RCA performed and concluded that a hose or a raw material was the problem.



Situation I w/ Data

Neutralization record from acidic waste cut from process used 40% more caustic, 5200 lbs, to neutralize the waste cut.

This equates to approx. 4700 lbs of excess HCl in system and approx. 4- 10 lbs of free iron.

Concluded that the bad load cell was responsible for the pink color
Cost of rework \$120K.

