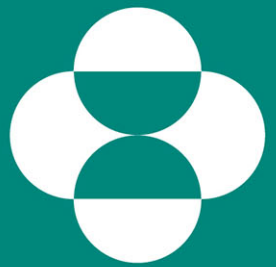
MERCK
INDUSTRIAL APPLICATIONS OF LIFE SCIENCE AND TECHNICAL DEGREES IN PHARMACEUTICAL DEVELOPMENT



MERCK

INVENTING FOR LIFE

03May2017

Welcome!

David Rossi (BS in ChE at JHU in 1998)

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Today's Agenda

- Welcome
- Presentation
  - Merck
    - Center for Material Sciences and Engineering (CMSE)
    - Chemical Commercialization & Technical Operations (CCTO)
    - BioProcess Technology Operations (BPTO)
    - Pharmaceutical Sciences and Clinical Supply (PSCS)
    - Women in Science and Engineering (WISE) Network
- Lunch
- Tour NJ Development Center (RY119)
- Group Discussions (RY119)

Merck: Our Company

VISION

To make a difference in the lives of people globally through our innovative medicines, vaccines, and animal health products. We are committed to being the premier, research-intensive biopharmaceutical company and are dedicated to providing leading innovations and solutions for today and the future.

MISSION

To discover, develop and provide innovative products and services that save and improve lives around the world.

http://www.merck.com/about/home.html#sthash.cRuCipdc.dpuf

Merck Key Company Facts

WHO WE ARE	Known as **Merck** in the United States and Canada, and **MSD** elsewhere
RICH HISTORY	Operating since 1851
BUSINESSES	Pharmaceuticals, Vaccines, Biologics and Animal Health
2016 REVENUES	$39.8 billion; 54% of sales come from outside the United States
2016 R&D EXPENSE	$6.8 billion; 24 programs in late-stage development; key areas: oncology, CV, diabetes, respiratory & immunology, neurology, infectious disease and vaccines
HEADQUARTERS	Kenilworth, New Jersey, U.S.A.
EMPLOYEES	Approximately 68,000 worldwide (as of 02Feb2017)

Merck's Global Presence

Canada
2%

US
38%

United States

LA
8%

Latin America

EMEA
32%

Europe, Middle East, Africa

AP
20%

Asia Pacific, Japan

Global headquarters in Kenilworth, New Jersey, USA

Public

MERCK
Be well

Merck – Where Patients Come First

"We try never to forget that medicine is for the people.

It is not for the profits. The profits follow, and if we have remembered that, they have never failed to appear."

- George W. Merck, 1950

Corporate Responsibility

"Merck is a pharmaceutical company with a soul." – Merck Sr. Vice President

Merck's Key Initiatives include:

- ***Merck for Mothers*** is a 10-year, $500 million initiative focused on creating a world where no woman dies giving life. We are committed to using our business and scientific expertise to improve maternal health and are already working in more than 30 countries around the world, including the U.S.

- To help address remaining barriers to HIV care, especially among underserved populations, the Merck Foundation launched a three-year initiative—the ***HIV Care Collaborative*** for Underserved Populations in the United States—to connect more people living with HIV to the care they need to stay healthy.

- The ***MECTIZAN® (ivermectin) Donation Program,*** for the prevention of river blindness, is the longest-running disease-specific drug donation program and public-private partnership of its kind, and is widely regarded as one of the most successful public-private health collaboration in the world.
  - William C. Campbell, a retired scientist from Merck Research Labs, was recently named the 2015 Nobel Prize winner in Physiology or Medicine for the discovery of avermectin, which led to Merck's development of Mectizan, a treatment for river blindness in Africa, Latin America and Yemen.

- Through the ***GARDASIL® Access Program***, Merck pledged to donate at least 3 million doses of GARDASIL for use in smaller-scale human papillomavirus (HPV) vaccination projects in eligible lowest-income countries around the world.

- ***Merck Patient Assistance Program***: The Merck Patient Assistance Program has provided Merck medicines free of charge to millions of eligible individuals who, without our assistance, could not otherwise have afforded them.

Prescription Products – A Diverse Portfolio

- •Cardiovascular / •Diabetes
- •Infectious •Disease
- •Respiratory / •Bone / Imm / Derm
- •Women's •Health
- •Oncology
- •Neurology
- •Vaccines

Recent Product Approvals

ZEPATIER™
(elbasvir and grazoprevir)
50 mg/100 mg tablets

KEYTRUDA®
(pembrolizumab) for Injection 50 mg

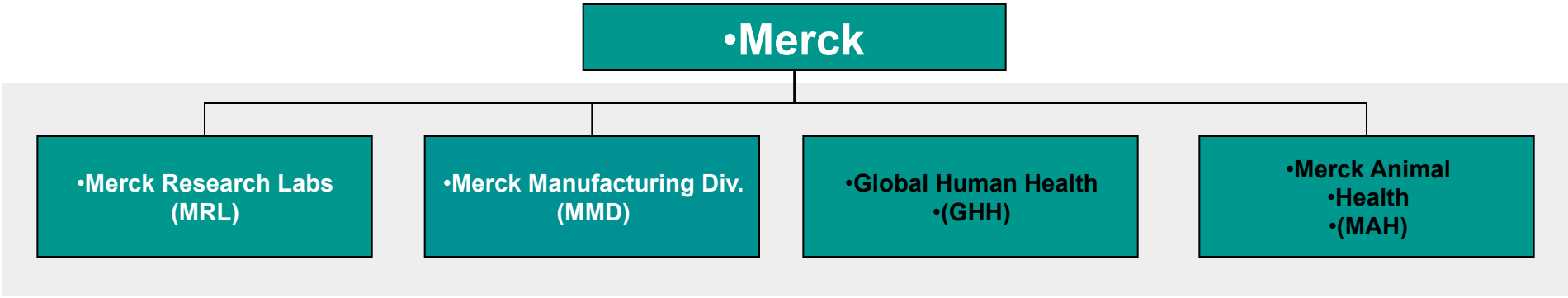
BRAVECTO®
(FLURALANER)

SIVEXTRO®
(tedizolid phosphate)
200 mg injection / 200 mg tablet

Belsomra®
(suvorexant) IV
5, 10, 15, 20 mg tablets

Cubicin® RF
(daptomycin for injection)
500 mg per vial

Merck's Four Major Divisions



•With a steady focus on innovation and sound science, we work to deliver vaccines, medications, and consumer and animal health products that can help millions around the world.

•Kenneth C. Frazier
•President & CEO

Therapeutic Focus Areas (human health):

- Oncology
- Diabetes
- Acute Hospital Care
- Vaccines

Center for Materials Science & Engineering (CMSE)

David Goldfarb, Ph.D.

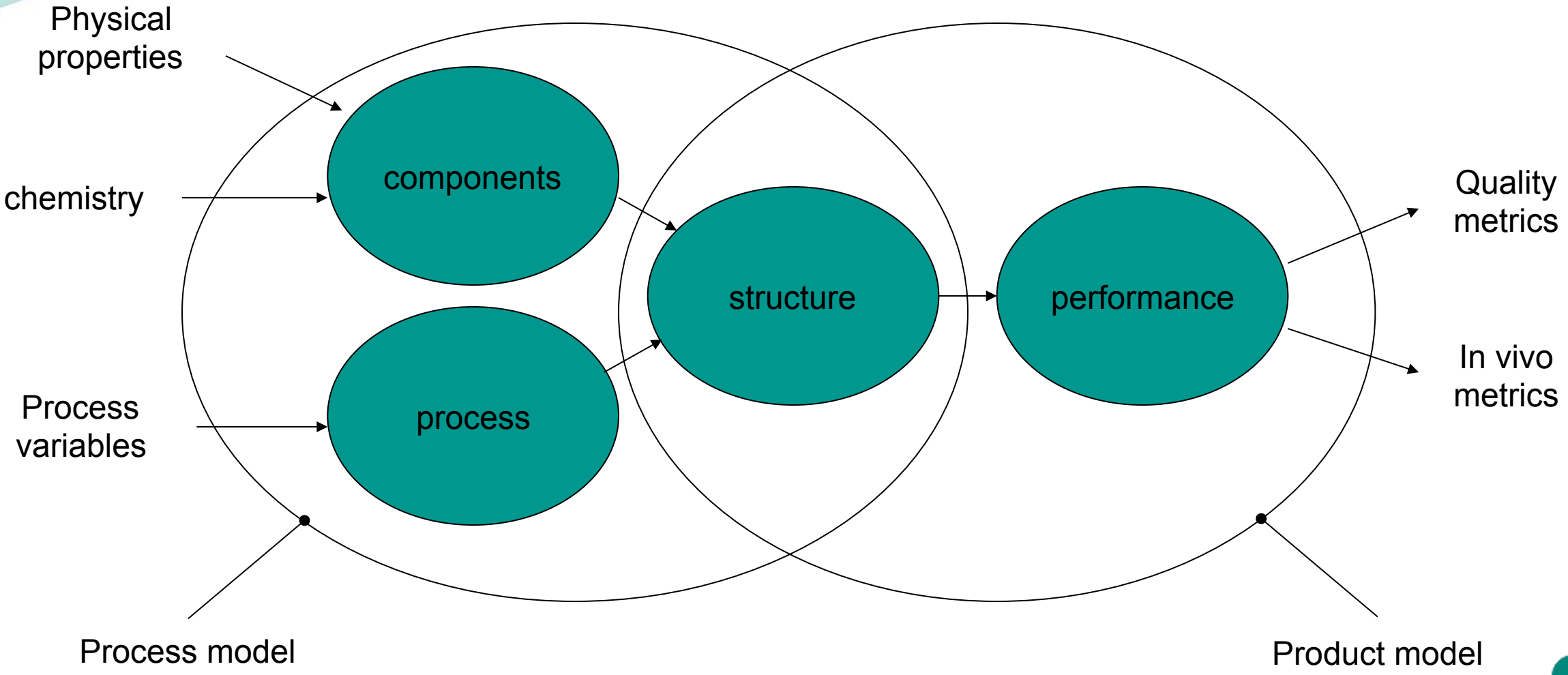
david.goldfarb@merck.com

Mission

- The Center for Materials Science and Engineering (CMSE) is a comprehensive materials science laboratory in MMD Science & Technology that serves Supply, Commercialization, and their partners.

- The Center supports development, troubleshooting, and optimization of products and processes through application of materials characterization and small-scale process experimentation.

CMSE Unifying Theme



CMSE Responsibilities

Pharm Process Development

- Develop characterization methods and provide data to support process development
- Identify product and process sensitivities to raw material physical properties

Supply

- Support manufacturing investigations
- Assess impact of material and manufacturing source changes; conduct product risk assessment and support vendor selection and change implementation
- Assess impact of process changes
- Support patent infringement and counterfeiting investigations

CMSE Labs

Imaging
- environmental scanning electron microscopy (ESEM)
- atomic force microscopy
- x-ray microtomography
- polarized light microscopy
- binocular 3D surface texture analysis, in ESEM
- NMR microimaging (H, P, Na)
- TEM
- AFM

Compositional Imaging
- micro-ATR FTIR microscope
- Raman microscope
- energy-dispersive x-ray (EDX) elemental analysis

Molecular composition, conformation, order, crystallinity
- FTIR (transmission, DR, PA)
- Raman
- UV-vis-NIR
- solid-state NMR (and EPR, off-site)
- x-ray diffraction
- LIBS

Phase behavior
- scanning calorimetry (DSC)
- isothermal calorimetry, with humidity controller
- thermal gravimetry (TGA), including mass spec. detection
- solvent and water vapor sorption
- solubility analysis (automated & manual)

Mechanical behavior
- thermal mechanical (TMA)
- uniaxial testing (wide speed-force range)
- dynamic mechanical (DMA)
- powder mechanical testing (FLODEX, shear cell)
- microindentation

Powder Characterization
- Particle size analysis (sieves, laser diffraction, DLS)
- Surface area analysis (BET – N2 and Kr)
- Volume analysis (Hg porosimetry, He pycnometry)

CMSE Labs (continued)

Rheology

- controlled stress rotational
- controlled strain oscillatory
- Brookfield
- solution capillary

Miscellaneous Analytical

- surface tension analyzer
- liquid density analyzer
- HPLC, MW analysis by (SEC-MALS)
- dissolution analysis
- “Lighthouse” headspace moisture analyzer
- KF
- GC-MS
- Leak detection (various)

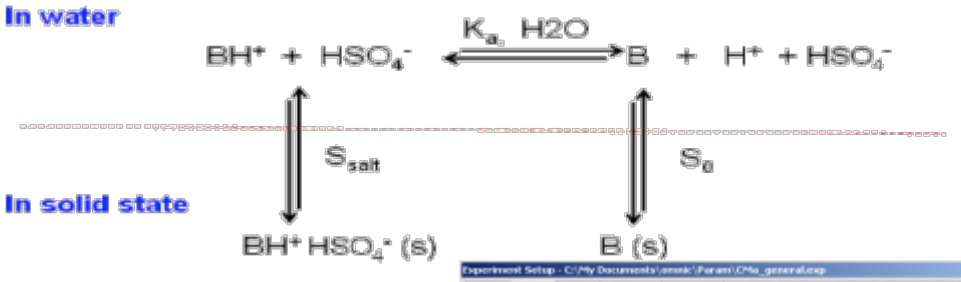
Process Equipment

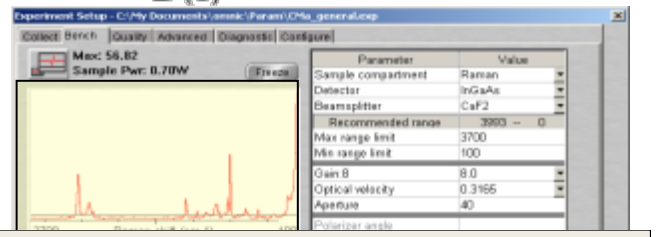
- Compaction simulator
- non-GMP pilot plant (various)
- temp/RH/photo stability ovens

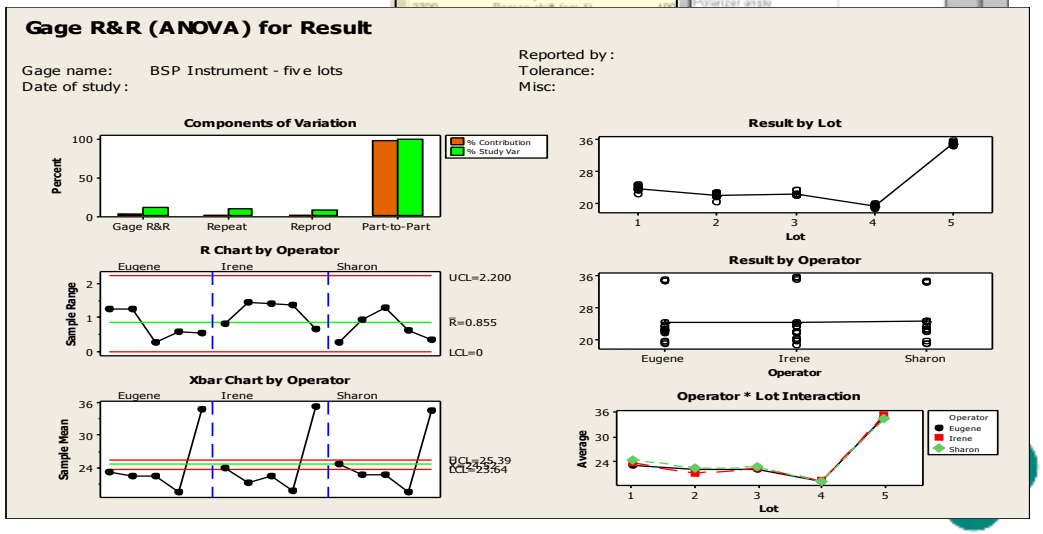
Pharmaceutical Development Support: Physical Methods Example

- **Physical Form Change (disproportionation)**
  - Evaluate FT-Raman and ssNMR methods sensitivity for drug product
  - Evaluate/improve GMP method Robustness via analysis of variance
  - Use method to quantify disproportion during drug product manufacture and storage
  - Defines product control strategy
  - Document in regulatory filing
  - Transfer method and train analysts and production/ stability sites

- **Others:** PSD, porosity/density, etc







Pharmaceutical Development Support: Characterization Example

High Shear Wet Granulation

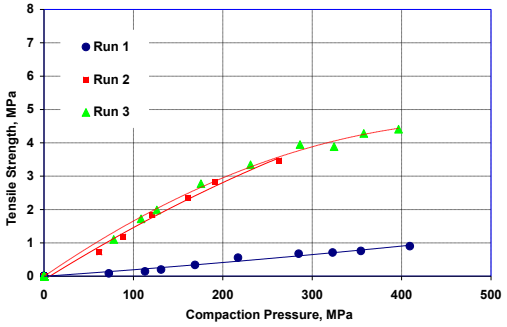
- Given drug product performance targets (dissolution, tablet elegance), determine controlling intermediate granule attributes
- Models/measure intrinsic API dissolution performance to assess clinical impact of RM
- Develop methods to probe, track and defining acceptance ranges for key intermediate attributes
- Monitor granule attributes as a function of scale-up, equipment configuration, and variability in raw materials
- Document design space or acceptance ranges in Regulatory Filing

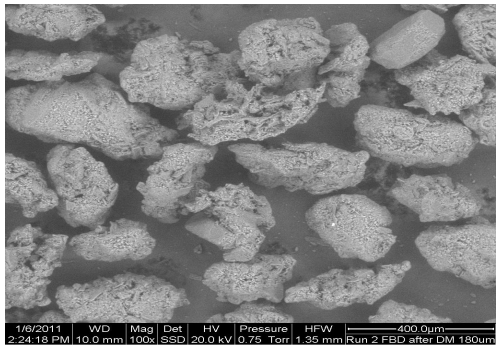
Others: Direct compression compactability, blend segregation and flowability risk assessment, etc

DOE

Run order	Factor 1 A: GFL	Factor 2 B: Wet Massing Time (minutes)	Factor 3 C: Impeller Speed (rpm)	Factor 4 D: Spray Rate
1	45%	5	500	High
2	25%	5	250	High
3	45%	0	250	High
4	45%	0	500	Low
5	25%	0	250	Low
6	25%	5	500	Low
7	25%	0	500	High
8	45%	5	250	Low

Attributes





Performance

Supply support

Responsibilities

- Support manufacturing investigations
- Assess impact of raw material, process and site changes;
- Support patent infringement investigations

Vision

- Characterize any structured material: raw, intermediate, product, packaging, process
- Be the materials expert or Formulator on the team. Apply (& seek) relationships between material physical attributes, processing and performance. Design, execute, and interpret bench- and pilot-scale pharmaceutical process experiments, and support full-scale work.

Challenge

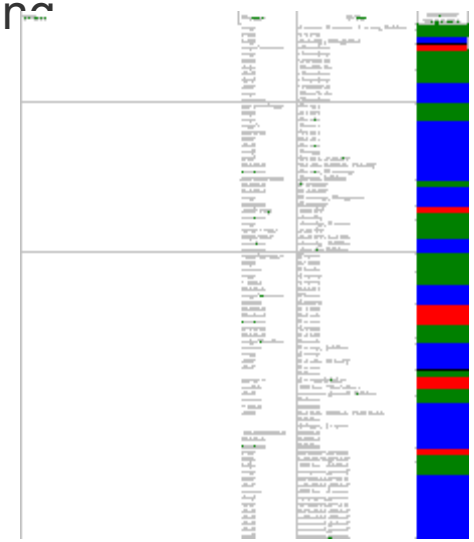
- We are 6 scientists supporting ~ 50 production sites + external, ~ 80 active ingredients, ~ 700 products, > 2000 raw materials and components, across wide technology/business areas: pharmaceutical, vaccines/biologicals, consumer care, packaging & veterinary.

  all analysis is custom

Supply support

Focus

- Customer service & communication within team structure
- Prioritization by impact, site relationship & study attributes
- Product knowledge management & use of technical resources/groups outside of CMSE
- Senior scientists, to independently handle complexity, highly focused science, multi-tasking
- Diverse expertise & broad instrument base



Supply support

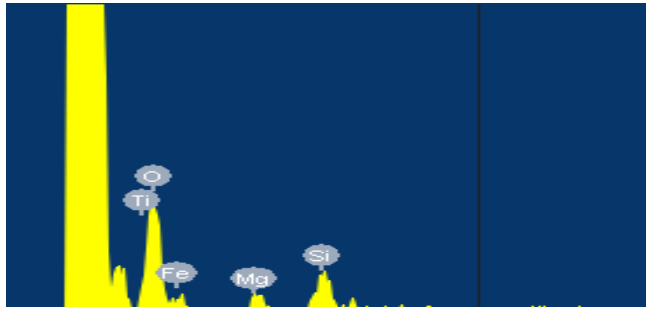
Examples of project work

- Site Transfer/Process Change Evaluation:
  detailed physical characterization; assess risk to pharmaceutical process and product

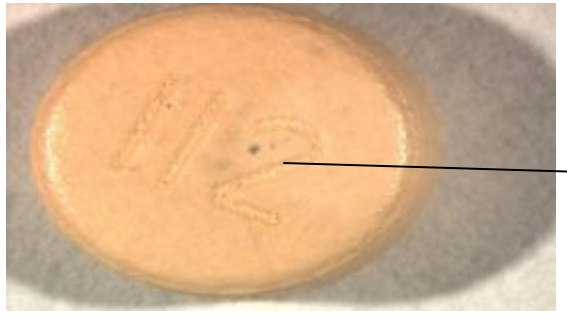
- Material Source Change Evaluation:
  assists with risk assessment; if deemed necessary, may recommend physical comparison of sources

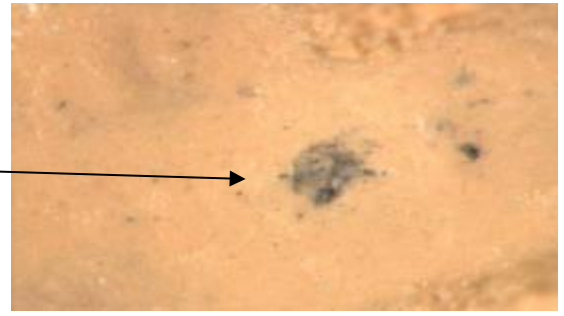
- Investigations / Troubleshooting/ Optimization:
  consult and participate on teams; contribute hypotheses; help devise or run experiment to define scope, test root-cause hypotheses, or identify controlling variables and mechanism

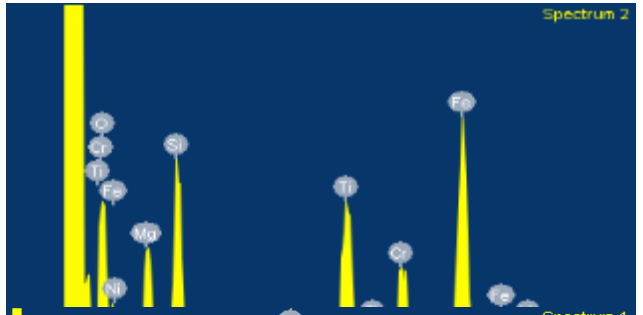
Example #1: Visual defects



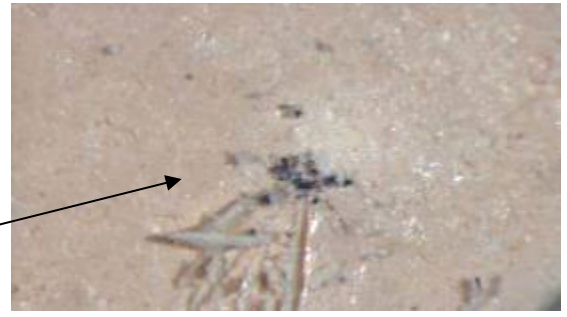
→ red iron oxide







→ stainless steel

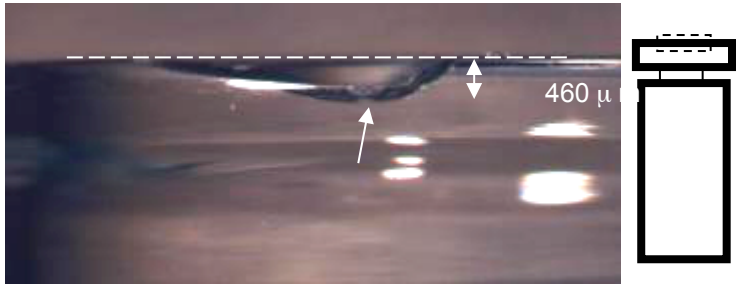


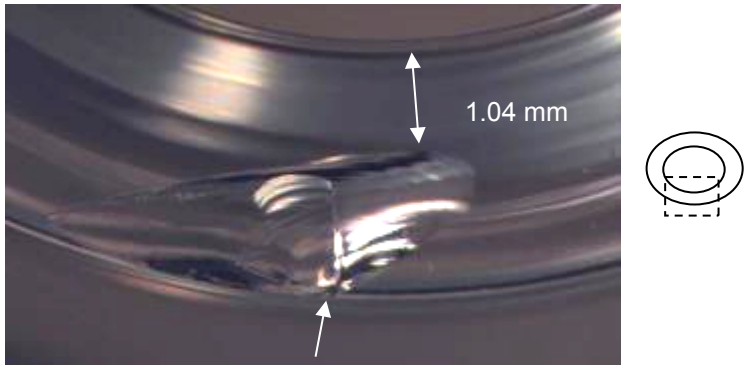
→ titanium

Example 2: failure mode analysis

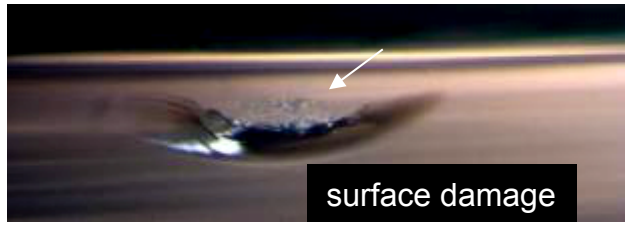
Problem: 2 mm glass chips found in final product. 100 lots quarantined

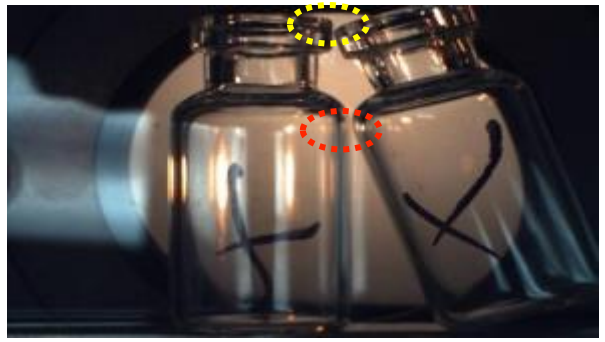
Preliminary investigation: vial top surface is the source; vial shoulders have check marks, some spaced 120°

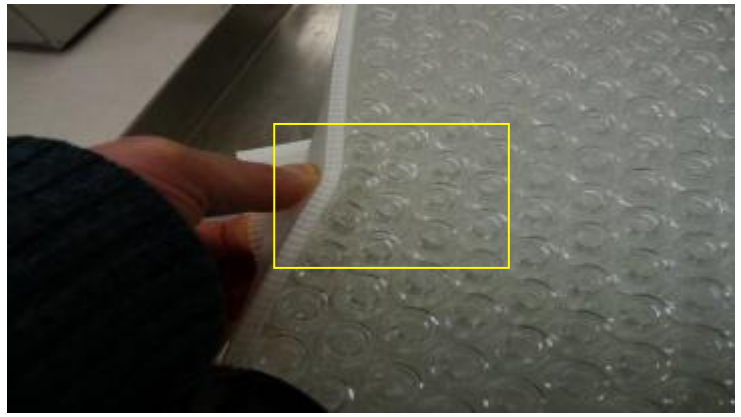




Deduced Mechanism: side impact







Root cause: package change by the vendor at Merck's request and for Merck's proposed package (from shrinkwrap to loosely packed corrugated plastic boxes);

Related work: study of integrity of vials with the chipped top

Chemical Commercialization & Technical Operations (CCTO)

Tim Maher (BS in ChE at RU in 1996)

Currently in Chem Commercialization and Technical Operations in Rahway, NJ. *tim_maher@merck.com*

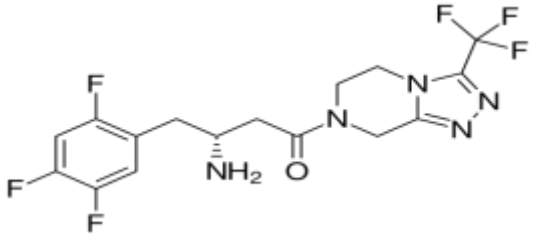
Chemical Commercialization & Technical Operations

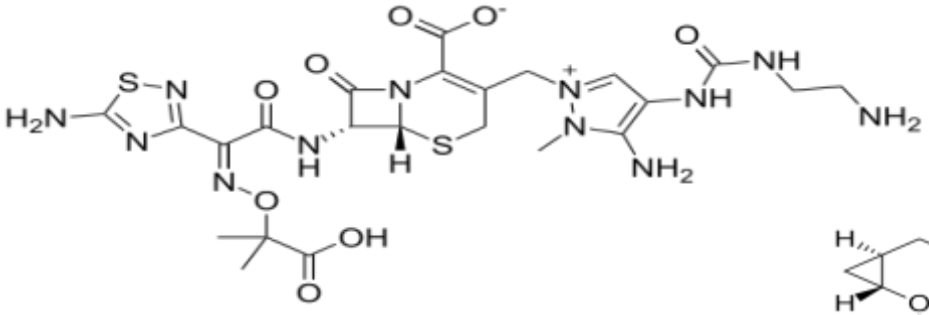
<u>CCTO is focused on Small Molecule Active Pharmaceutical Ingredients;</u>

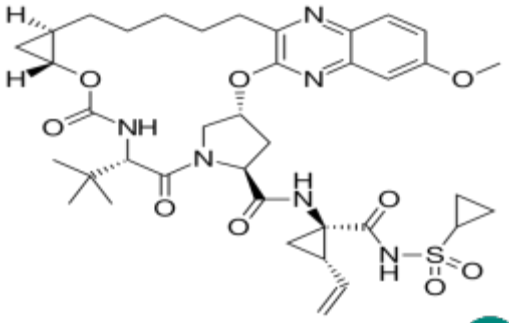
Approved Products & Late Stage Development Projects

•Chemists and Chemical Engineers that are responsible for

- Technical Leadership
- Process Improvement
- Problem Solving
- Technology Transfers
- Process Characterization
- Manufacture at External Partner sites







My Career (API Development & Operations)

- 1995 – Graduated Rutgers, BS ChemE; started in Merck ChemE R&D
- 1995 – Engineer for *Crixivan* (1st wave of effective HIV treatments)

  Pilot Plant production of API for clinical trials & compassionate use, Factory Startup, Process Startup, De-bottlenecking

- 1997 – Project Engineer (*Emend*; anti-depression → anti-emetic drug)

  Developed, Improved, & Piloted different steps of the API synthesis

- 1998 – Rahway Pilot Plant Operations, Safety & Environmental Projects, Capital Projects
- 2006 – Project Leader – responsible for development API entire projects
- 2011 – External Partnerships for late development APIs

Typical CCTO Activities

- Entry-Level – BS/MS/PhD – likely assigned to a Late Development Project

  Process Development Labwork & Rangefinding (Merck labs & external)

  DOEs & Statistical Analysis

  Regulatory Filing Authoring/Support

  Example – experimental labwork and modeling to understand the process and operational limitations for a new antibiotic API

- Experienced Employee
  - Responsible for all approved products at a partner's site
  - Data-mining for Process Stability, New Process Introductions, Process Improvements, Process and Equipment Changes

    - *Example – 10kgs/year of specialty anti-emetic, or 50MT/year of API for diabetes*

BioProcess Technical Operations (BPTO)

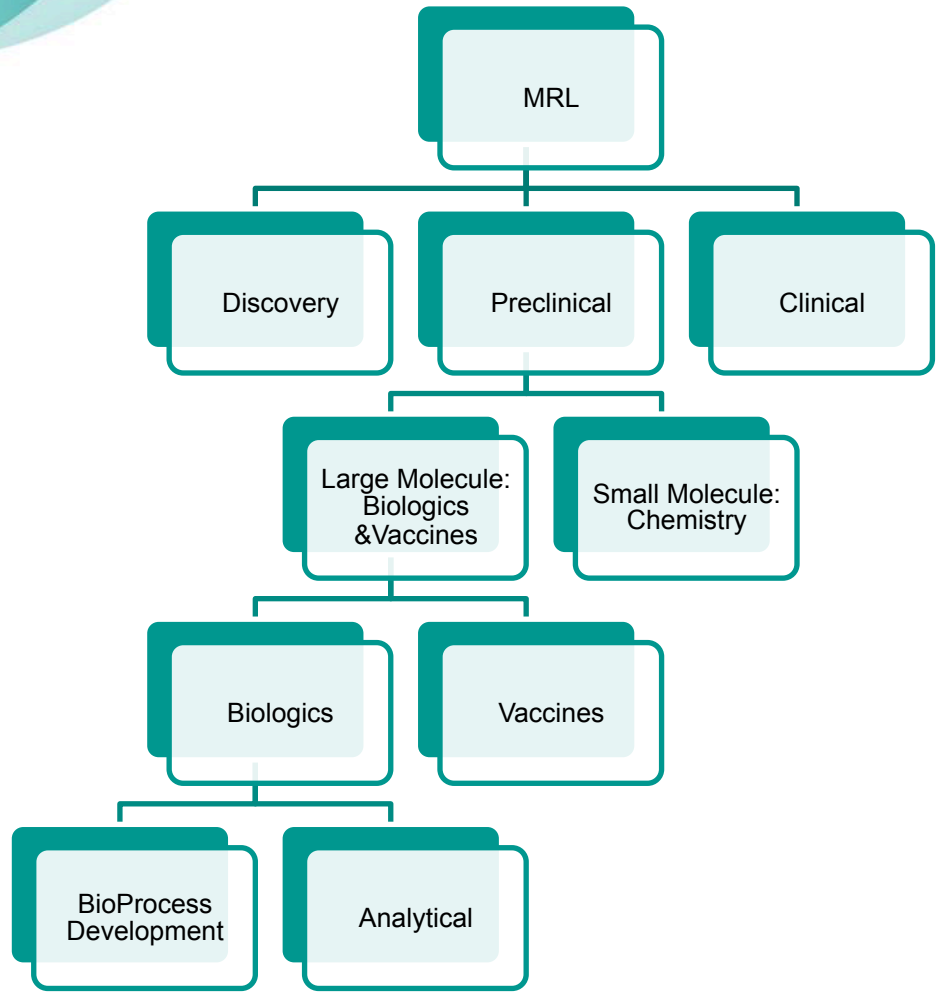
Kristin O’Neill (BS in ChE at RU in 1996)

Currently in Chem Commercialization and Technical Operations in Rahway, NJ. *tim_maher@merck.com*

BioProcess Overview

- MRL- BioProcess Development
- BioProcess Technical Operations
- My Story

BioProcess Development – What is it and where does it fit in?



- Occupy the space between discovery and commercial manufacturing
- Large space
  - Time
  - Scale

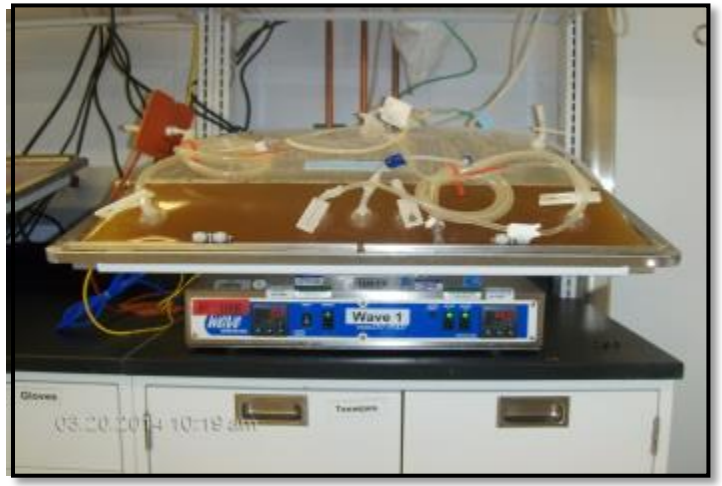
- Supports
- Cell line development
- Process Development (Drug Substance)
  - Upstream and Downstream
- Formulation Development (Drug Product)
- Pilot scale operations
- Clinical manufacturing

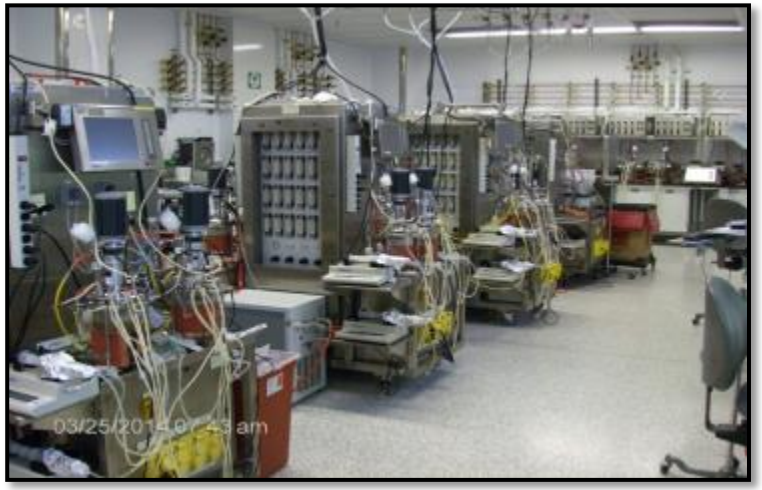
BioProcess Technical Operations

- **Mission:**
- Support the development of robust, cost-effective production methods and technologies by ensuring reproducible unit operations from
  - Initial seed vial thaw and inoculum expansion
  - Bioreactor scale-up
  - Harvest through purification

- **Vision:**
- Operational excellence applied to the optimization and technology transfer of biologics drug substance processes for the preparation of recombinant proteins and antibodies. This includes supporting
  - Clone selection
  - Medium development
  - Process scale translation
  - Production of pre-clinical drug substance supplies
  - Knowledge management
  - Technical data/information manipulations
  - Statistical data analysis
  - Quality-by-design strategies

•Ensuring Reproducible Unit Operations





- Inoculum scale-up
- Reagent supplies for MAbs and recombinant proteins
- Support medium optimization and upstream process development

•Operational Excellence and Technical Support

- Support and build on upstream scale-up and facility fit studies
- Preclinical production of drug substance
- Technical and operation support for upstream clinical and commercial manufacturing and tech transfer activities

- Robust,
- Cost-Effective
- Deliveries

- Support scale translation of harvest process development
- Pilot scale primary recovery and purification
- Capabilities for controlled freezing of drug substance for toxicology supplies

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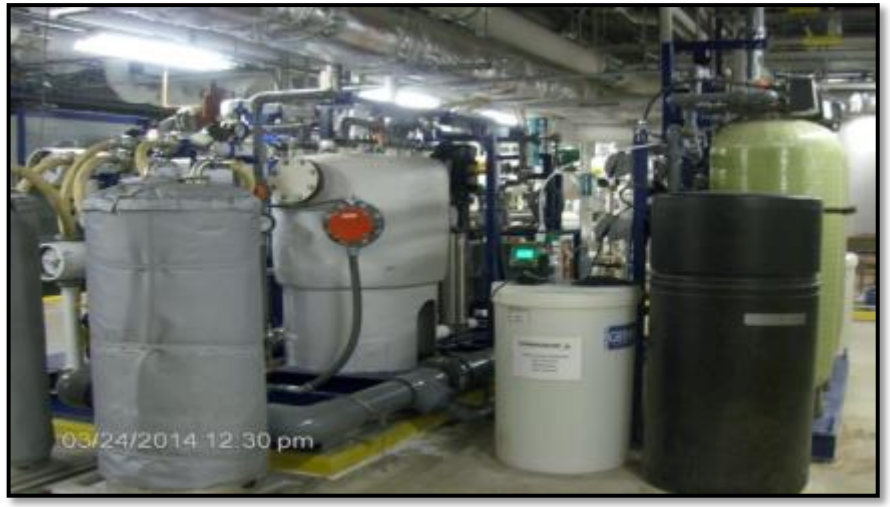
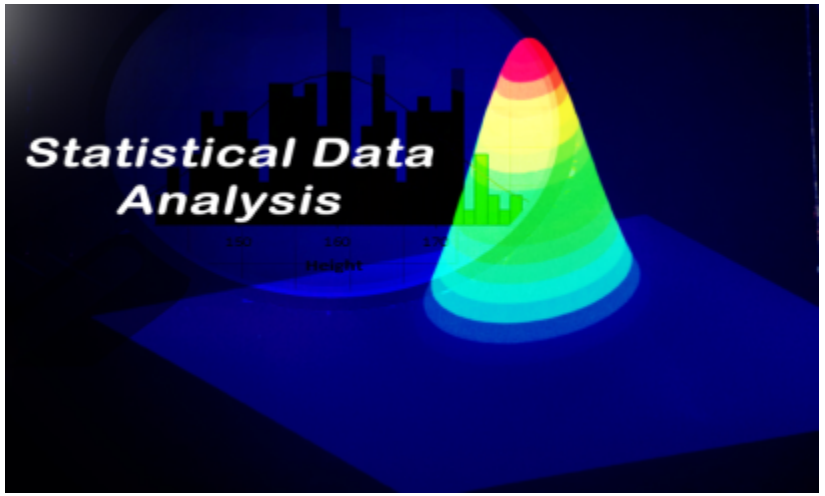


OPERATIONS SUPPORT

- Maintenance of Biologics equipment and systems
- Oversight of capital projects and funding
- Maintain and support clean utilities, HEPA, HVAC, and production support systems

Business and Process Development Technologies Support

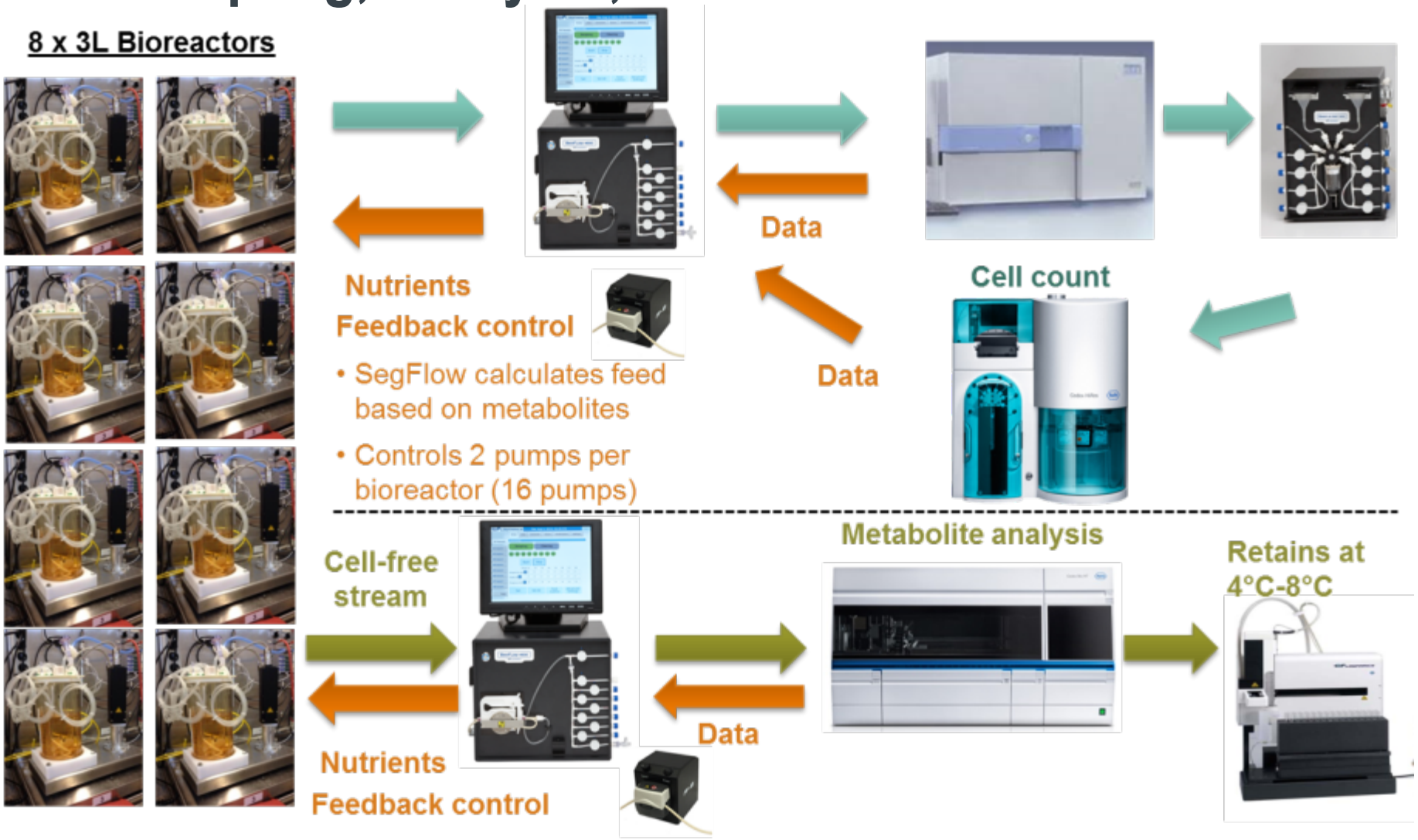


- Provide statistical guidance on the analysis of large data sets
- Support preparation of Regulatory Filings
- Support implementation of QbD and strategic improvements in Knowledge Management

My Story

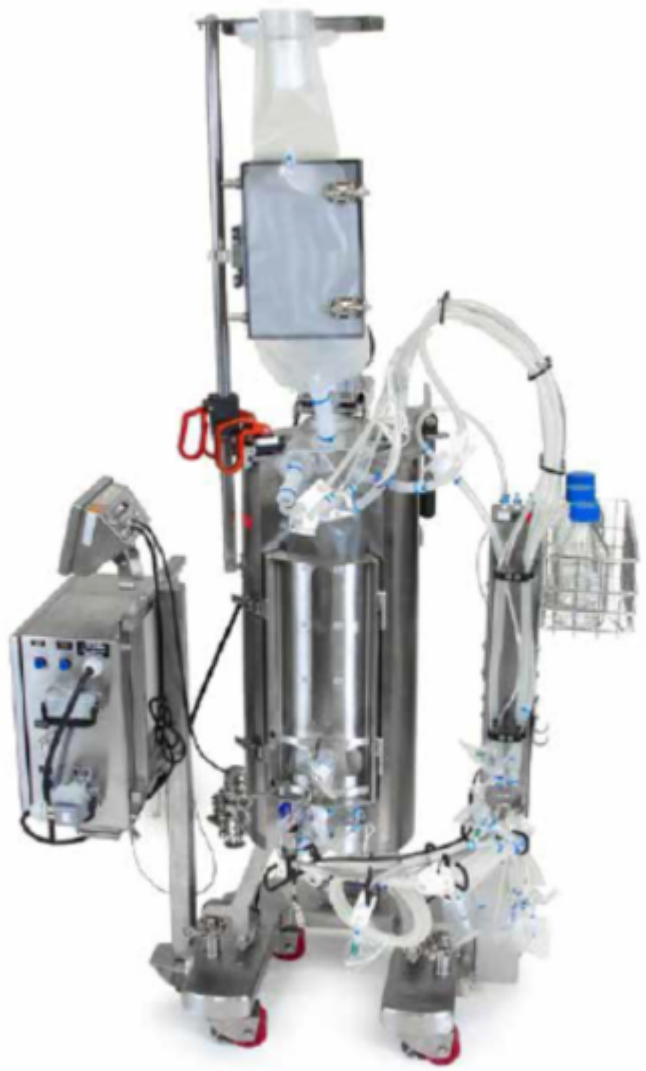
- Chemical Engineer (B.Ch.E, M.S.) by training
- Work as Biochemical or Bioprocess engineer
- 12 years within BioProcess Development and Merck supporting upstream processing
  - Experience with mammalian, yeast, and bacterial culture from 15mL to 12,000L
  - Started off in upstream process development running experiments in shake flasks and bench scale reactors
  - Lead upstream engineer for 500-1000L non-GMP pilot plant
  - Led upstream tech transfers for PhI to PhIII clinical manufacturing campaigns
  - Supported regulatory filings
  - Bioreactor tank characterization studies – gas transfer and mixing time
  - Supported new technology implementation and capital projects

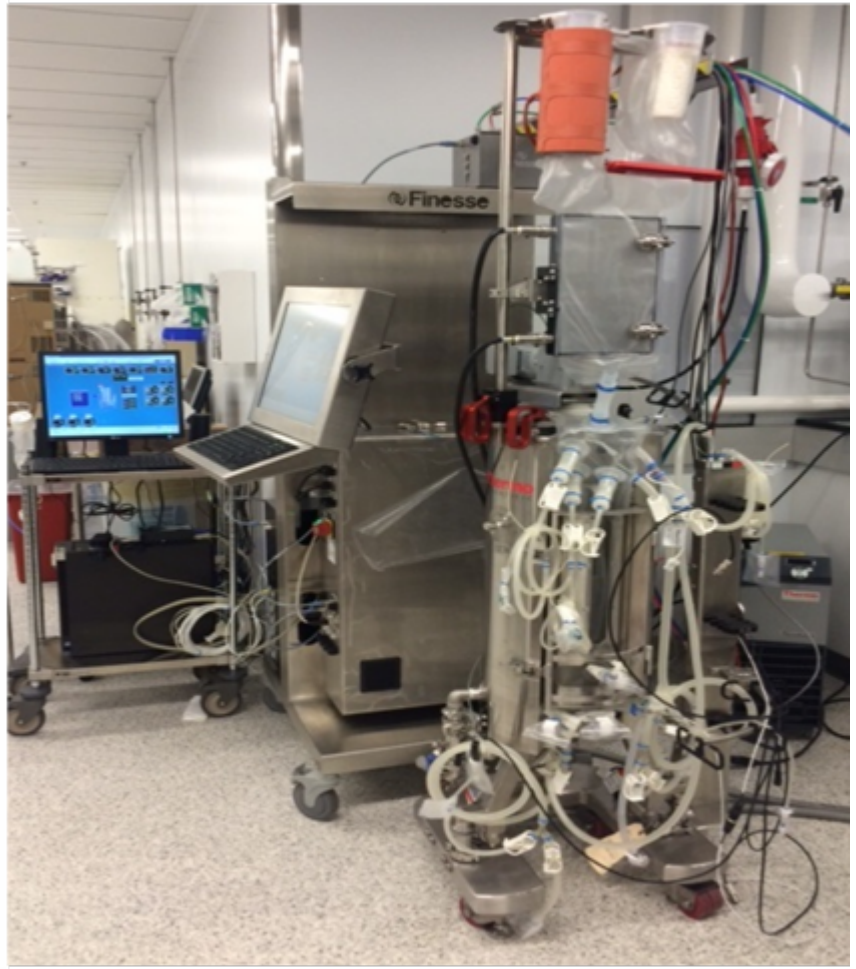
Automated Sampling, Analysis, and Feed Control for 3-L Bioreactors



Single-Use Fermentation

	30L S/S	30L SUF
Sparger type	Open pipe	Drilled Hole
Airflow range	0-40 slpm	0-60 slpm
Oxygen Supply	N/A	2 mass controllers
Oxygen ranges	N/A	0-30, 0-50 slpm
Foam probe	N/A	Foam probe
Vent Filters	1x 0.2µm	2x 0.2µm
Vent condenser	Aux chilled water	Separate refrigeration unit
Temperature	Jacketed, pressurized closed-loop system	Jacketed: separate TCU unit
Pressure Range	0-15 psig	< 0.5 psig
Vessel Sterilization	SIP at 122° C for 30 minutes	Gamma radiated
Peripheral Sterilization	Pre-sterilized in autoclave, attached by SIP, single use connectors and by sterile tubing welding	Pre-sterilized in autoclave, attached by sterile tubing welding and single use connectors
Media Addition	In-situ sterilization/Filter sterilized	Filter sterilized
Agitator type	Rushton	Rushton
Number of impellers	3	3
Impeller spacing	4.5"	6.0"
Impeller diameter	4.0"	3.5"
Number of blades	6	6
Blade height	0.75"	0.70"
Number of baffles	4	4
Operating range RPM	150-900	55-600
Controller/HMI	GE fanuc PLC and SCADA	Finesse G3 Pro DeltaV controller
pH and dissolved oxygen probes	1x sterilized in-situ	2x autoclaved then aseptically attached





Pharmaceutical Commercialization Technology (PCT)

David Rossi (BS in ChE at JHU in 1998)

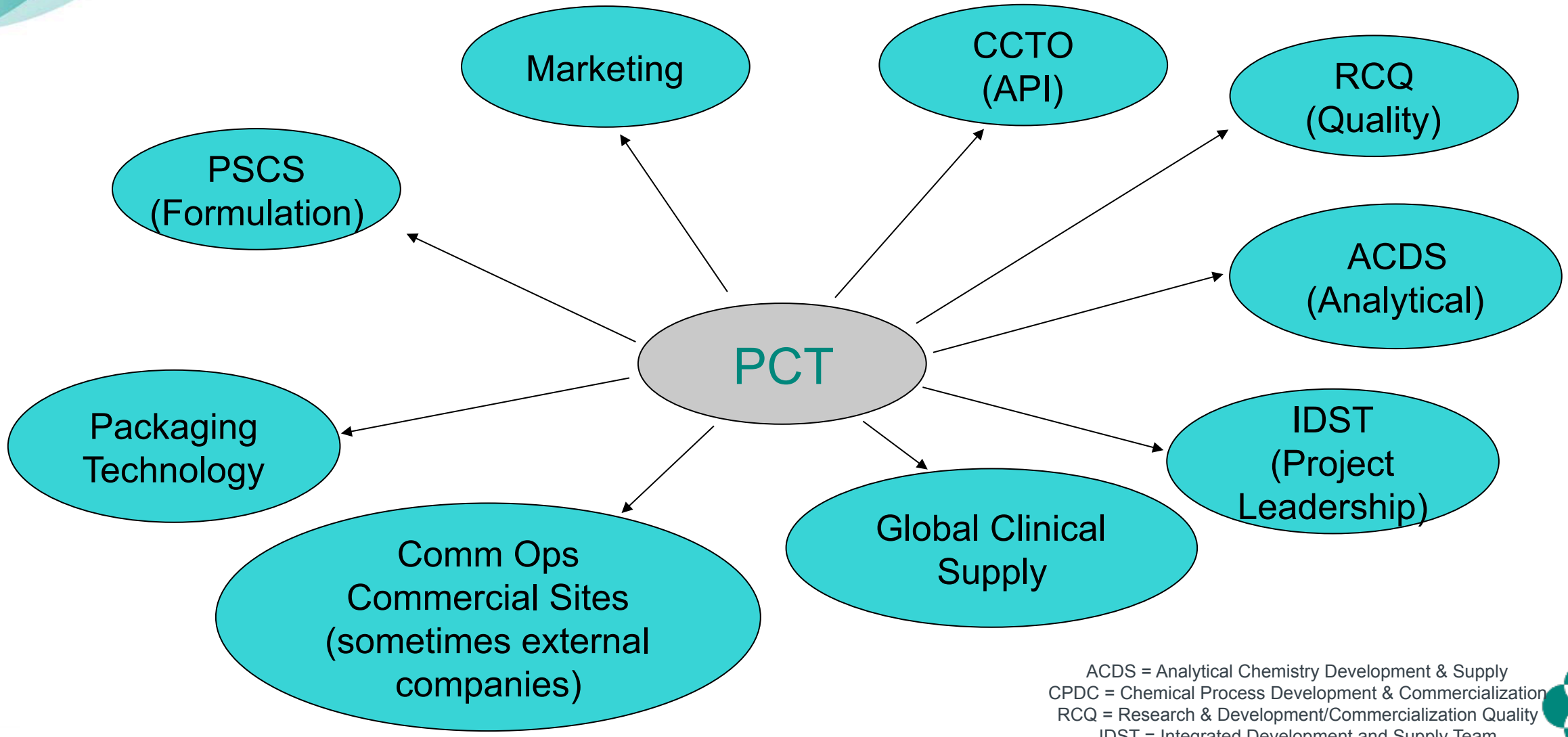
Currently in PCT , Rahway, NJ.
david.rossi2@merck.com

PCT Mission

- We develop manufacturing processes, prepare regulatory file content, and are responsible for launching non-sterile drug products, specifically oral dosage forms.
- Our products:
  - Begin with small or large molecule API*
  - Most typically are:
    - Tablets
      - standard (IR and ER)
      - orally disintegrating
      - chewable
    - Capsules
    - Oral solutions/suspensions
    - Powders for reconstitution

*API = active pharmaceutical ingredient

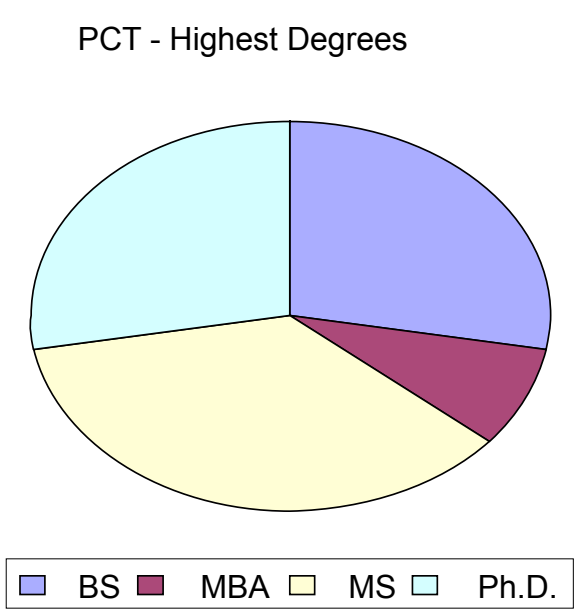
Key Partner Relationships

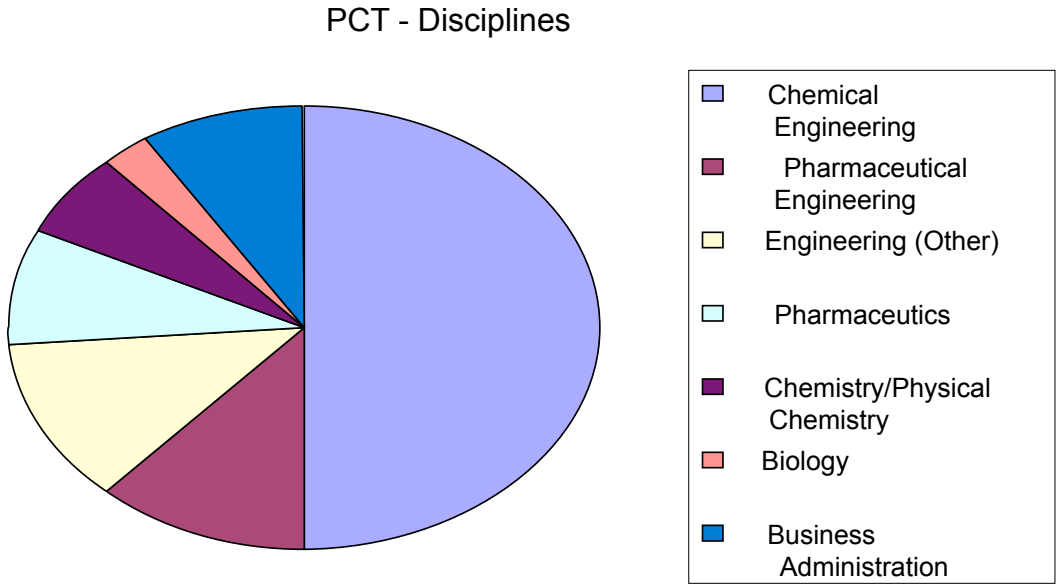


ACDS = Analytical Chemistry Development & Supply
CPDC = Chemical Process Development & Commercialization
RCQ = Research & Development/Commercialization Quality
IDST = Integrated Development and Supply Team
PSCS = Pharmaceutical Science and Clinical Supply

PCT Colleagues

- Currently ~ 68 people (WP & NJ)
- Chemical Engineers, Pharmacists, Chemists (organic, physical), MEs, and Material Scientists
- Mix of BS, MS, and PhD
- Wide range of experience levels





•PCT staff data from 2013

A Day in the Life of a PCT Engineer/Scientist

- **Planning & executing lab experiments** to support process development (with an eye on what will be written in the filing)
  - Documentation of experiments – reports/memos
- Participating in **cross-functional teams** responsible for decision-making and project implementation
- Coordinating **preparation of clinical trial and stability materials** through collaboration with Commercial Operations
- Author clinical phase filings (IND, IMPD), and registration filings (NDA, MAA, others)
- Supporting the **transfer of robust & scalable manufacturing processes** to a network of internal and external manufacturing facilities
  - Knowledge transfer to site technical reps
  - On-site support to development, validation, and launch batches

Formulation Science

David Harris, Ph.D.

david.harris@merck.com

Formulation Science

Formulation = Active Drug + Inert Excipients

Necessary to ensure the drug is:

- Chemically & physically stable
- Available to the body after administration
- Manufacturable

Broad scope:

- “Small molecules” – molecular weight < 1000
- Macromolecules - peptides / proteins / antibodies
- Vaccines

Formulation Science

- Develop formulations for human clinical trials
  - Phase I → Phase II → Phase III
- Develop intended commercial formulations
  - Ensure stability, bioperformance, manufacturability
- Transfer formulation & manufacturing process to downstream manufacturing groups
- Write sections of regulatory applications for product
  - NDA (New Drug Application), submitted to US FDA, etc

Formulation Science

Who?

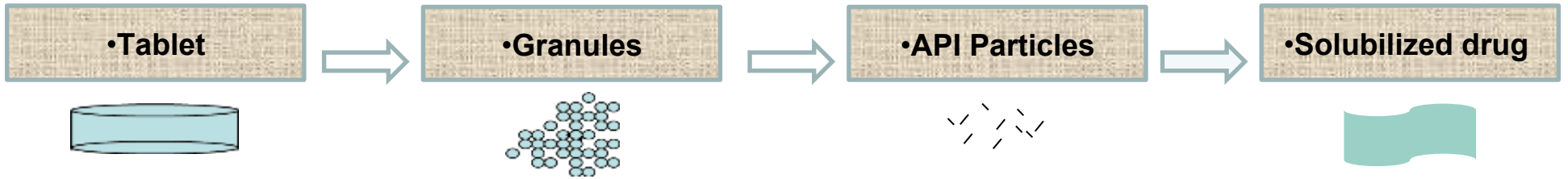
- Highly collaborative network of scientists / engineers
- Degrees: B.S., M.S., M.B.A., Ph.D.
- Majors:
  - Biochemistry
  - Chemical Engineering
  - Chemistry
  - Materials Science
  - Mechanical Engineering,
  - Pharmaceutical Sciences
  - Pharmacy

What?

- Making & testing prototypes at laboratory scale
- Data analysis / statistics
- Problem solving
- Experimental design
- Technical writing
- Manufacturing trials at pilot scale / commercial sites
- Project management
- Understand patient / customer needs

Technical Challenge

- Long-term trend towards drug molecules with lower water solubilities
  - Drug must dissolve in stomach / intestine before it can be absorbed



- Necessitates use of more complex formulation technologies to “enable” drug delivery
  - Solid Dispersions
    - Single-phase dispersion of drug in water-soluble polymer
    - Prepared by spray-drying or hot-melt extrusion
  - Particle size reduction
    - Reduce drug particles to micron-size (1-10µm) or sub-micron size
    - Increases surface area for dissolution to occur
    - Significantly more difficult to process, assure stability of finer particle size materials

WOMEN IN SCIENCE & ENGINEERING

Advancing Science + Engineering Through Inclusion & Diversity

Introduction to WISE

Sonali Bhatnagar

May 2017

Merck

- **Merck Among Top 50 Employers for Female Engineers**
- Merck has been recognized by Woman Engineer magazine, the most widely read recruitment magazine for female engineers. Merck was selected by readers of Woman Engineer magazine who indicated the top companies in the country for which they would most like to work or whom they believe would provide a positive working environment for women engineers.
- In the spring issue of Woman Engineer magazine, Merck is listed as No. 19 on their list of the Top 50 Employers for female engineers.

•Merck Earns Place on 2017 List of Top Companies for Executive Women

•Merck is one of 60 companies recognized by the National Association for Female Executives

•The National Association for Female Executives (NAFE) was founded in 1972 and is one of the largest women's professional associations in the United States.

•The NAFE Top Companies for Executive Women recognizes corporations and nonprofit organizations that have moved women into top executive positions and created a culture that identifies, promotes and nurtures successful women.

WISE Background/Mission

WISE Background

- WISE was formed in late 2011 to support the advancement of women in science and engineering within GSTC.

Mission:

- WISE will drive and influence culture and champion changes resulting in:
  - an environment in which females are supported to reach their full potential
  - Increased visibility/awareness of the needs/benefits for gender balanced leadership teams within GSTC which will maximize business results for GSTC globally leading to a HPO
- We will achieve this by
  - Providing visibility and linkages to other women's groups in Merck and providing complementary support to those groups for women in GSTC (i.e. mentoring)
  - Providing best practice and networking forums for women in scientific and technical roles Developing and driving initiatives that aim to enhance awareness at all levels of the benefits afforded by a gender balanced organization

•There are only 13 women CEO's running Fortune 500 companies. That's only 3%!

Questions?