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# Satisfying Both Clinical Supply and Process Development with a "State-of-the-Art" Kilo Lab Facility

*by Edward Kobelski, Thomas Staigers, and Charles Sullivan*

**This article presents a unique approach of building a facility to be used both for process development and scale-up, and for manufacturing of APIs for clinical supply. It outlines the project challenges, the particular design solution implemented to meet this challenge, and all of the client's needs.**

## Introduction

Pfizer, one of the world's largest pharmaceutical companies, is focused on discovering, developing, and manufacturing cost-effective human and veterinary therapeutics based on an intensive R&D commitment. This year, Pfizer will spend close to $5 billion on its R&D budget in search of its next pharmaceutical break-through. To aid in their search for new drug candidates, Pfizer scientists continually strive to implement the latest advancements in technology through state-of-the-art facilities and equipment.

This dedication to drug discovery and development was further demonstrated with the completion of a state-of-the-art Exploratory Development Supply Facility (EDSF) at the Pfizer Global Research and Development site in Groton, Connecticut - *Figure 1*. The primary function of the EDSF facility is to synthetically prepare, scale-up, and deliver high quality bulk intermediates and finished good quantities of Active Pharmaceutical Ingredients (APIs) in a safe and expeditious manner within a cGMP environment to support drug safety and Phase I and Phase II clinical trials.

In order to help meet these objectives, Pfizer contracted Process Facilities Inc. (PFI) to engineer, design, commission, and qualify the facility; ADP Marshall Construction Co. was contracted to construct the facility. The project required the renovation of Pfizer's existing development facility located in Groton, Connecticut. The project occupies approximately 15,000-sq. ft. of the existing building. The project provides 12 individual cGMP development laboratories in 9000 sq. ft., and 6000 sq. ft. is dedicated to the installation of state-of-the-art kilo scale laboratories to support Pfizer's R&D requirements.

*Figure 1. Pfizer's state-of-the-art Exploratory Development Supply Facility in Groton, CT.*

## Project Challenge

Preparation of drug substance to support drug research programs provides an interesting range of challenges. In addition to the need to scale laboratory procedures on untested chemistry and react to the as-yet undiscovered vagaries of behavior at scale, the need to protect individuals and the surrounding environment is critical to the successful operation of the research business. Facility design

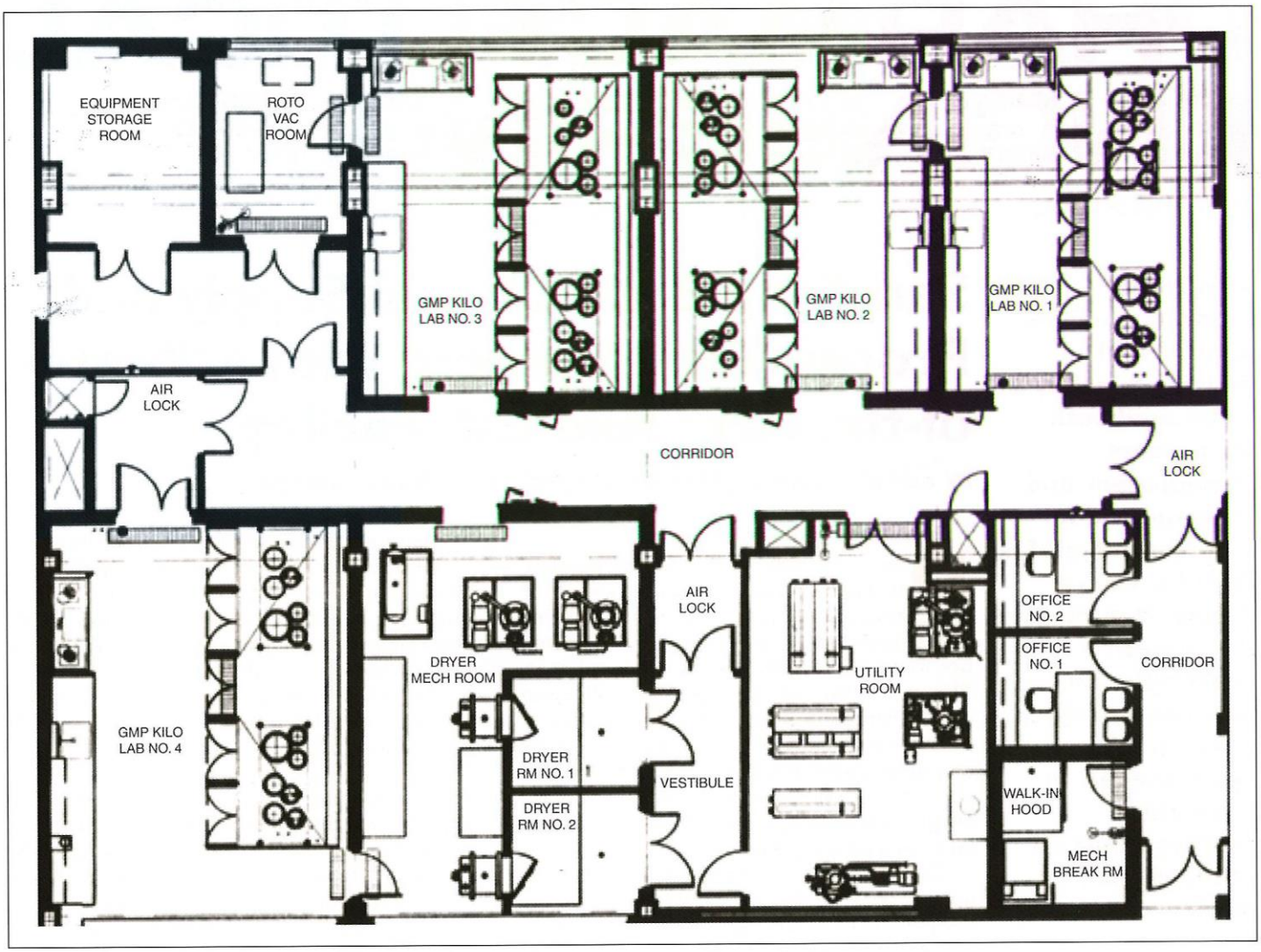



*Figure 2. The four production suites each contain two reactor suites.*

in this aspect of the industry must allow for flexibility in operations, while maintaining a high standard of personal and environmental protection. Superimposing the regulatory framework of cGMP compliance into this mix heightens project complexity, requiring a highly integrated design approach, involving a substantial range of disciplines.

Traditionally, the previous facility was able to accomplish scale-up activities from a laboratory scale (flasks up to 22 liters) to pilot plant scale (chemical reactors starting at 50 gallons) without problems. However, the missing link was the transition of batch chemistries from the relatively simple stirred glass flask to the industry standard hard piped chemical reactor. This transition created some concern among development chemists since these processes were still relatively new and required maximum chemist control and observation. In addition, there was an equipment "gap" between 22 liters and 50 gallons that was not being serviced. Consequently, reactions exceeding laboratory scale would typically be diluted to obtain adequate agitation in a 50 gallon reactor and then after a tailored work-up, concentrated and brought back to the laboratory for isolation. This practice consumed countless gallons of solvent, was expensive to staff, and more importantly, resulted in a significant loss of precious development time.

In order to accommodate the chemists' concern of control and observation, the existing Preparations Laboratory proposed use of manual control for process valving and glass overheads for maximum visual observation. This solution created some concern with pilot plant personnel relative to safety, specifically involving glass overhead piping. Also, chemical exposure was high on the list of project concerns. Due to the unknown characteristics of some of the novel molecules encountered at this stage of drug development, engineering safeguards had to be developed to mitigate contact of scientists and these materials. Somehow, a reasonable solution to satisfy this range of needs would have to be found.

## Project Mission Statement

Based upon the above challenges, Pfizer assembled a team to develop a reasonable and effective solution. The Pfizer team was composed of chemists and engineers representing research, operations, safety, facilities, QA, and environmental. The team's directive was to develop options and recommend a path forward to create an EDSF that could safely and visually bridge the transition between the reaction flask and the conventional hard piped chemical reactor. Pfizer management issued the team the following policy statement concerning safety and cGMP compliance relative to this specific project to help guide them to a successful conclusion:

> ***The challenge for the team was to match these process requirements with the limited space available in the existing building.***

"All chemical operations (open or closed) must be carried out in enclosures or hoods within processing suites. Enclosures or hoods are to contain all glass processing equipment. Suite boundaries constitute cGMP applications. Wet cakes will be isolated in the enclosures or hoods, placed in sealed containers, and transported to the individual dryer suite for drying."

The team then established the overall requirements for the facility by developing the following mission statement for the project:

### *Mission Statement*

The New Exploratory Drug Supply Facility must:

1. provide a safe working environment for Pfizer development scientists
2. provide a cGMP environment for API supply
3. improve development capabilities of the chemical process
4. bridge the equipment gap
5. satisfy safety concerns relative to glass systems
6. fit the proposed facility into the existing building - envelope
7. minimize disruptions to current development activities

## Programming the Solution

Once the mission statement had been established, Pfizer enlarged the project team to include appropriate design disciplines including architecture, process technology, and project management. The team met initially for about a week to benchmark and establish concepts and options. The early work focused on the existing building to be utilized and determination of the most appropriate area that could be considered for the project. Once the options for available spaces were identified, the team focused on process considerations.

The initial process discussions centered on actual chemistries to be employed, materials of construction, reaction conditions, unit operations, and quantities required. The primary process concerns involved safety and equipment suitability as defined below:

- Safety
  - potential energy of the individual materials employed
  - potential energy of the various reaction mixtures
  - toxicity of the individual materials employed
  - toxicity of the intermediates produced

- Equipment Suitability
  - equipment types and capability
  - material of construction
  - equipment size or capacity
  - environmental protection

The challenge for the team was to match these process requirements with the limited space available in the existing building. It was this limited space that ultimately governed the number and size of the processing systems considered. Based upon the above programming, the following minimum project requirements were established:

### *Facility*

- four independent kilo lab suites, one with air lock
- each suite to contain one well-ventilated enclosure for the reactor systems and one 6 ft. bench top fume hood
- minimum of 100 fpm face velocity with two doors open in each well ventilated enclosure
- two reactor trains of varying size in each well ventilated enclosure
- minimum of 5 ft. operating space between reactor systems in the well-ventilated enclosure
- two independent dryer suites complete with laminar ventilation
- damage limiting construction (wall relief panels)
- build out area to have dedicated HVAC
- breathing air system available in all process areas
- existing utilities reused whenever practical
- dedicated mechanical areas

### *Process Equipment*

- eight reactor trains
- reactor sizes 50 to 200 liters
- reactor bottoms glass-lined carbon steel or Hastelloy C
- reactor tops, overheads, condensers, and receivers constructed of glass
- 1 to 10 Kg of solids produced per batch
- batch temperature capability of -20°C to +150°C with optional -100°C and +200°C
- full vacuum to atmospheric pressure operations
- glass feed tanks required for each system
- reactor systems to be easily cleanable (all wetted surfaces visible)
- reactor systems should be flexible with reactor bottoms replaceable
- reactor batches easily sampled

*Figure 3. Five sets of double doors to each kilo lab provide full frontal access.*

- portable product isolation devices
- two vacuum shelf dryers each with 50 liter wet cake capacity
- two portable (and flexible) scrubbing devices
- rotary evaporator with 50 liter capacity
- process vacuum pumps capable of 1 torr deadheaded at the pump

## The Resulting Facility Design

The final facility configuration contains four kilo scale production suites, two dryer rooms, two mechanical areas, one rotary evaporator room, as well as other support areas. The mechanical and drying areas are situated central to the production suites. One main corridor provides access between the suites, mechanical areas, drying rooms, and evaporator room while storage and office areas are located out of the high traffic areas with its own corridor. These corridors provide efficient personnel and material flow patterns.

### *cGMP Design Considerations*

The protection of the product from potential contamination was a primary concern during design. The projected handling activities of the product from raw material through finished New Chemical Entity (NCE) were examined from a possible contamination viewpoint. This included a complete examination of material handling, equipment, and facility interaction during product preparation. The resulting design ensured all materials, batch mixtures, and product would be exposed to the environment only in very controlled areas.

These areas were identified and then engineered to yield a facility that could maintain product purity in conjunction with appropriate regulations, design standards, and operating staff expertise.

### *Suites*

The four production suites in *Figure 2* each contain two reactor systems that are located inside a containment enclosure. Each suite is approximately 23 ft. deep by 19 ft. wide and isolated from the other areas on the floor by two-hour fire rated and blast resistant walls. The suites are sized to comfortably accommodate two to three technicians and are equipped with 16' of bench space, complete with a large sink for rinsing and washing large glassware. In addition, a 6-foot bench hood is included for smaller chemical operations. Each suite is equipped with a breathing air station.

The doors to the suites are a "door in door" design including a smaller swing out door inside a larger sliding door. This unique feature saves critical floor space, since it allows larger openings without having to adhere to code requirements typical of large swing out doors, such as recesses and unobstructed egress. The smaller door is used for daily personnel access, while the large doors allow for large equipment removal.

In addition, suite #4 is complete with an air lock and shower for additional containment and safety. The enclosure specific to suite #4 also is equipped with a HEPA type filter (with "bag in - bag out" containment features) to prevent any dust escape to the environment.

### *Enclosures*

Each kilo lab suite contains a well-ventilated laminar flow containment enclosure, approximately 22 ft. wide by 6 ft. deep and 10 ft. high. The enclosures each house two separate reactor systems, approximately 8 ft. wide by 3 ft. deep and 11 ft. high. The reactor systems are situated at opposite ends of the ventilated enclosures, positioned to allow full front, rear, and side access. Approximately 5 ft. of free space is available between the two reactor systems for placement of portable equipment and large raw material containers (i.e., lever paks, drums, etc.). The enclosures are a walk in type of stainless steel construction with five sets of double doors for full frontal access - *Figure 3*. Utility stations are located inside each enclosure for connection of portable equipment and for cleaning. Airflow is to be once through in sufficient volume to maintain a face velocity of 100 fpm with one set of doors open. A unique feature to this design is the center access space. Because of the unique downflow air design, this space can be occupied with the doors open even during processing operations. The airflow in this central area is intentionally designed to provide substantial airflow away from personnel breathing zones in order to maximize protection of scientists working in this area. This feature enables the area to be used for a wide variety of unit operations, which could potentially generate dusts, fumes, or mists, maintaining a safe environment for operating personnel.

### *Dryer Suites*

Two identical tray dryer rooms are provided in a central location to the kilo lab suites off an independent corridor, which

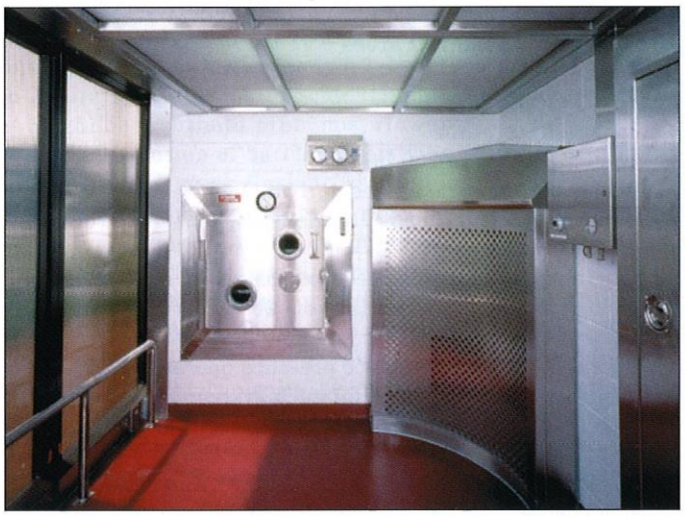


*Figure 4. Curved exhaust manifolds complement the HEPA filtered downflow ceiling design.*

*Figure 5. Temperature and vacuum control of the reactor systems is accomplished via vacuum and TCU skids located in the mechanical rooms.*

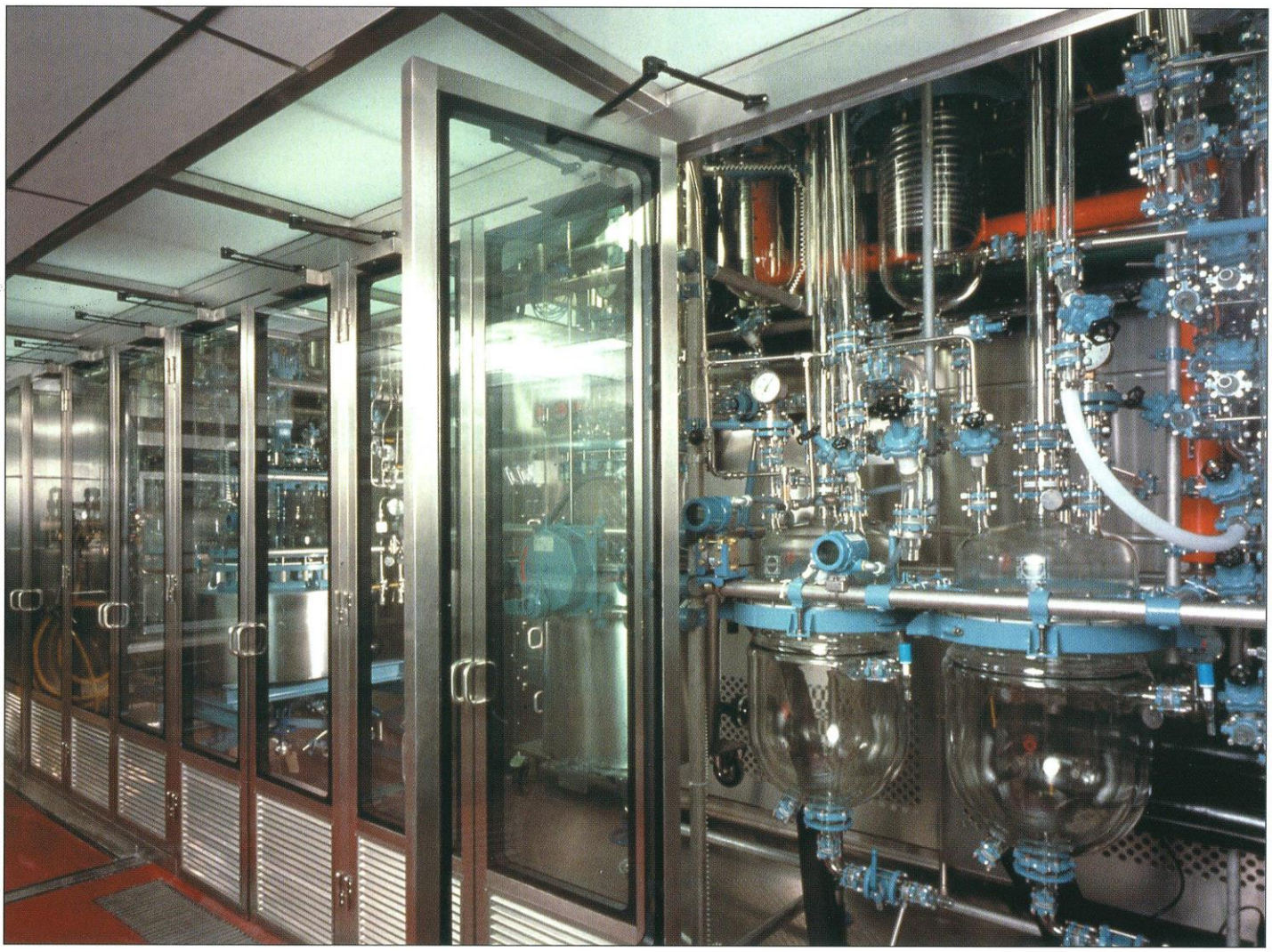


*Figure 6. The Buchi systems are located entirely within downflow booth enclosures to protect the operator from exposure to dangerous solvents.*

also serves as an air lock. The dryer rooms are 9 ft. deep by 7 ft. wide and protected by two-hour fire rated and blast resistant walls. Access to each suite is via 5 ft. wide double doors. The dryer room itself is constructed to act as a walk in hood. The entire ceiling is a downflow plenum. Curved exhaust manifolds are located in convenient corners for safely loading and unloading product drying trays - *Figure 4*. The exhaust also is equipped with a HEPA type filter to prevent any dust escape to the environment. The dryer rooms are equipped with breathing air stations and utility stations for equipment cleaning.

### *Mechanical Rooms*

The support equipment for all suites is located in two mechanical rooms - *Figure 5*. The first room contains the dirty side of the tray dryers, as well as the supporting dryer vacuum pump systems. This room also contains the Temperature Control Unit (TCU) for one of the production suites equipped for high temperature service as well as two specific area hoods for routine maintenance and change out of the dryer room air filters.

The second contains the balance of the TCU systems for the production suites and the two dryer systems TCUs. Also contained in this room are the two process vacuum systems and the roughing vacuum system. Similar to the first mechanical room, this room also contains two specific area hoods for routine maintenance and changing the air filters.

The equipment in each room is arranged such that operator or maintenance access is provided for a minimum of three sides, and in most cases all four sides.

## The Resulting Process Design

There are eight installed Buchi reactor systems; two per walk-in enclosure - *Figure 6*. Reactors one through six are glass-lined carbon steel and the other two are constructed of Hastelloy 276 C. Two enclosures contain 50 and 100 liter systems while the third contains a 100 and 200 liter system. The forth enclosure contains two 75 liter Hastelloy 276 C vessels. All of the reactor systems are accompanied by two round glass or conical receivers and two glass feed tanks. The reactor systems are able to process at temperatures between -20°C to +150°C utilizing a glycol single liquid temperature control system. Refrigerated glycol at -20°C is supplied to each reactor TCU where it can be heated via a steam-heated heat exchanger and pumped through a closed loop to its specific reactor to achieve temperature set point requirements. To support reflux and distillation requirements, each reactor will have glass shell; tantalum coil condensers serviced with chilled water for (+5°C) operation. Vessel operating pressures will range from full vacuum to atmospheric.

Two of the reactor systems are set up slightly different. One has an independent high temperature thermal fluid heating system allowing it to have a temperature range of -20 to 200°C. The other has the capability of isolating and draining its jacket glycol system and replacing it with liquid nitrogen injection system allowing the reactor to reach temperatures as low as -100°C. These vessels have the same operating pressures and vacuum capabilities.

Both dryer systems are vacuum shelf dryers of Hastelloy construction and are located in independent suites. Each dryer is approximately 2 cu. ft. with four shelves. Heating and cooling is accomplished utilizing dedicated glycol single fluid temperature control units with an operating range between 25 and 90°C. Each dryer also has a dedicated vacuum system capable of achieving 4 torr in the dryer. Vacuum, heating, and cooling equipment is located in an adjacent mechanical room along with the back of the dryer. Only the operating end (door end) of the dryer is located in the dryer suite. Product will be manually loaded and discharged.

### *Emission Control*

Emissions from the facility are controlled with the use of refrigerated vent condensers (-20°C) and portable fume scrubbers. Each reactor pair can be vented to a dedicated vent condenser prior to release to environment or to a portable scrubber. The scrubbing units provided are of glass construction to maximize compatibility of a variety of scrubbing media (e.g., bleach, caustic, or solvent-based scrubbing mixtures). Vacuum is generated via recirculating liquid ring pump systems using the ring fluid as scrubbing media. Inadvertent liquid discharges are captured via a spill containment system.

### *Process Control Discussion*

The process control system consists of Allen Bradley (A-B) SLC5 and/or PLC5 series Programmable Logic Controllers (PLCs) and personal computer/CRT based operator workstations. A number of PLCs are provided and located in the Kilo lab suites and process subsystems being controlled. These PLCs are networked over a DH+ data highway to permit a high-speed exchange of data with a central supervisory computer system. CRT based operator workstations are provided local to the process subsystems being controlled.

The PLCs will provide I/O for discrete and analog signals, processing capabilities to perform discrete/sequential control logic, and analog/continuous control logic functions, and DH+ communication interface functions. A PLC came as part of the chiller package performing control and monitoring functions over equipment and devices within that chiller package. Additional PLCs were custom designed and installed to perform control and monitoring functions for the balance of the process systems as well as to perform any coordinated control (sequential and/or continuous) over selected vendor packages. The PLCs execute control ladder logic designed by the package equipment vendors and by the control system integrator. A standardized approach to packaging of data within each PLC for communication over the DH+ data highway was developed to ensure each PLC will communicate alarms, equipment status, and analog values completely and efficiently. Communication of control signals, interlocks, and shutdown signals over the data highway were minimized. The data highway is used predominately for passing data from the local PLCs to the operator interface workstations.

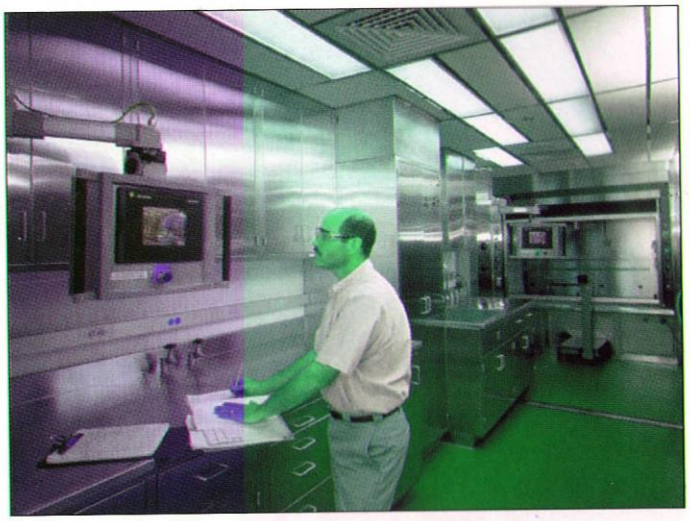


*Figure 7. An operator takes readings during the commissioning and qualification of the control system.*

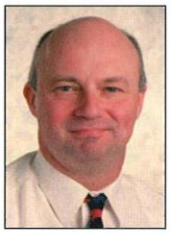
The local operator interface workstations are CRT based and provide the necessary local operator interface. The workstations shown in *Figure 7* provide the local operator with conventional controller type faceplates, pushbutton stations, status indications, custom interactive graphic displays, and local alarm processing and trending. These local operator workstations are the primary operator interfaces for control and monitoring of the various processes.

## Summary

The kilo lab fills a unique niche for the Pfizer development staff, but it does so while recognizing the physical limitations of the reactor systems. The kilo lab was constructed on the philosophy that it would operate as an extension of the laboratory. By accepting this rationale, the parameters of the proposed chemistry are required to be highly scrutinized. The pressure rating of the systems is approximately 0.4 bar and as a measure of safety, Pfizer scientists conscientiously set the bursting disc pressure at 0.2 bar. Extreme care needs to be employed during the inertion sequence of the operation so that over-pressurization does not occur. Pfizer accepts the inherent limitations of the reactor systems, and safeguards the facility and its personnel by requiring SOPs for reactor system operations, including proper vessel inertion and safety data on all processes proposed to be scaled in the EDSF. Every process slated for the kilo lab undergoes a process safety analysis and equipment compatibility review. All isolated intermediates and products have as a minimum Differential Scanning Calorimeter (DSC) testing performed before the process is approved for scale-up. Depending on the results of the DSC, additional testing such as Accelerating Rate Calorimetry (ARC) or Reaction Calorimeter (RC-1) may be required. Considerable effort is employed by the Process Safety and Engineering Laboratory (PSREL) at Pfizer before a process is allowed to be scaled in the Kilo lab. It should be noted that these tests are typically the minimum to be performed. Test samples are normally submitted for safety testing during the "early" stage of development so that the scale-up in the kilo lab is not subjected to delays in test scheduling.

The EDSF has changed the early development philosophy at Pfizer. The ability to visually witness chemical and physical changes during a process is intriguing. The gains over the last three years have certainly outweighed the risks. There has been a significant reduction in processing time, partially due to the reduction in solvent consumption, which equates to enormous savings when the cost of handling "side streams" is considered. Coupled with the ease of cleaning, visibility, versatility, and cost savings, the most important variable that the kilo lab has saved is time -- precious development time.

## About the Authors



**Edward A. Kobelski** is a Group Director in Pfizer Global Research and Development's Groton site, and is responsible for bulk organic synthesis operations in the Exploratory Development Supply Facility and the Pilot Plant. With more than 20 years of experience in the design and operation of organic synthesis scale-up facilities, Kobelski was the Project Principal for the conceptualization and design phases of the EDSF project. Following this experience, he then served as Process Engineering Director for Pfizer's newest state-of-the-art pilot plant facility in Sandwich, UK, and has recently relocated back to the Groton site. Kobelski received a BS in chemical engineering in 1978 from the University of Connecticut, an MS in business administration from the Hartford Graduate Center in 1992, and is a member of the American Institute of Chemical Engineers.

**Thomas Staigers** is the Supervisor of the EDSF at the Pfizer Global Research and Development site in Groton, CT. Staigers received a BS in biology from Southern Connecticut State University in 1983 and started at Pfizer in 1984. Staigers has held a number of laboratory positions at Pfizer that have focused on the scale-up of bulk intermediates and API. During the design and construction phase of the manufacturing facility, he served as a principal architect for the process design before his promotion to EDSF Supervisor in 1998. Currently, he manages the daily operations of the facility and ensures that process safety measures are implemented and followed. Additionally, Staigers oversees operations to ensure the chemical processes are conducted within Standard Operating Procedures defined by cGMP guidelines.

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**Charles Sullivan** is Vice President of Process Technologies and Principal of Process Facilities, Inc. (PFI), an Architectural/Engineering/Construction/Validation firm focused in the pharmaceutical industry with offices in Boston, Philadelphia, and San Francisco. Sullivan is responsible for process technologies of chemical APIs for the firm, and has more than 30 years of experience in the design and operation of organic synthesis laboratories, scale-up, and manufacturing facilities. Sullivan was PFI's Process Technology lead for the conceptualization and design phases of the EDSF project. He also has performed similar roles for kilo labs for such clients as Amgen, Bayer, and Vertex. Sullivan received a BS in chemistry from the University of Rhode Island. Prior to joining PFI, Sullivan was responsible for the operation of kilo labs, pilot plants, as well as full scale manufacturing with Wyeth-Ayerst and Novartis. Sullivan is a member of both the American Institute of Chemical Engineers and ISPE.

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