Walk Through Survey Report
of
Eli Lilly & Company Research Labs
Indianapolis, Indiana

Survey Date:
March 28, 1980

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Date of Report:
June 26, 1980

Industrial Hygiene Section
Industry-wide Studies Branch
Division of Surveillance, Hazard Evaluations and Field Studies
National Institute for Occupational Safety and Health
Cincinnati, Ohio

PLACE VISITED:	Eli Lilly & Company Research Laboratories Indianapolis, Indiana
DATE OF VISIT:	March 28, 1980
PERSONS(S) CONDUCTING SURVEY:	George Carson Larry Elliott Seth Pauker David West
EMPLOYER REPRESENTATIVE:	Irving Johnson, V.P. of Research (317) 261-4391
UNION:	None
STANDARD INDUSTRIAL CLASSIFICATION OF PLANT:	2834 - Pharmaceutical Preparations
PURPOSE OF SURVEY:	To investigate and evaluate Eli Lilly's methods of containment, environmental monitoring, and health surveillance for production/research processes utilizing recombinant DNA techniques.

ABSTRACT

A walk through industrial hygiene survey was conducted at the Eli Lilly and Company Research Laboratories in Indianapolis, Indiana on March 28, 1980. This company is involved in research and development of recombinant DNA fermentation processes applicable to pharmaceutical preparations. Assessments of control technology, including containment design, validation procedures, and work practices were made during this visit. Recommendations for a worker registry, preventive maintenance program, and controls to minimize potential hazards to the worker are included.

INTRODUCTION

The public debate over genetic engineering has focused on the possible hazards of genetically modified microorganisms, potential health hazards to workers involved with industrial application of recombinant DNA techniques, and the utilitarian prospects of such technology. Several risks assessment programs designed to investigate some of the characteristics of proposed host rector systems which might affect hazard potential have been conducted by interested scientist. Likewise the benefits from recombinant DNA technology are being as vigorously promoted. The National Institute for Occupational Safety and Health (NIOSH) is responsible for conducting research, recommending occupational safety and health standards, providing technical assistance to workers and employers, and conducting training and educational programs. NIOSH's responsibility extends to both existing and emerging technology which might impact on worker health and safety. Thus, NIOSH is evaluating the potential occupational hazards involved with recombinant DNA technology.

This research effort was prompted by the anticipated surge of recombinant DNA techniques in various industrial processes. Genetic engineering technology may be utilized in various manufacturing processes in the areas of agriculture, organic chemicals, energy, food processing, and pharmaceuticals. This potential growth and the possibility of uncharacterized occupational exposures indicate the necessity for careful evaluation of health risks. NIOSH is accustomed to examining new technologies for potential occupational hazards and developing recommendations for safeguarding the workers health. Implementation of safeguards and protective engineering controls early in the growth of an industry can only minimize human suffering and avoid expensive retrofitting of production systems.

Under the Occupational Safety and Health Act of 1970, Public Law 91-596, the National Institute for Occupational Safety and Health (NIOSH) was mandated and authorized to conduct research and health studies. Specifically, Section 20(a)7 states that NIOSH shall conduct and publish industrywide studies of the effect of chronic or low level exposure to industrial materials, processes, and stresses on the potential for illness, disease, or loss of functional capacity. Thus, this research is pursuant to the development of health standards applicable to a braod range of occupational environments. In compliance with this mandate, the Industry-wide Studies Branch of the Division of Surveillance, Hazard Evaluations and Field Studies is conducting a study to assess the potential occupational hazards in research and the commercial application of recombinant DNA technology.

In order to analyze the current technology for potential occupational hazards, NIOSH plans to conduct several walk through surveys of recombinant DNA processes and associated industries. Identification of potential hazards, with recommendations to minimize worker exposure, will be derived from the information gained during these surveys. This report contains recommendations relevant to operations at Eli Lilly and Company. Recommendations applicable to the entire industry employing recombinant DNA technology will be made after NIOSH completes a thorough assessment. An assessment of the following areas will be made:

- process operations with attendant potentials for worker exposure
- engineering controls (e.g. physical containment design, ventilation, exhaust gas filtration, waste product controls, etc.)
- validation procedures (e.g. of sterilization, physical containment, and process termination
- work practices
- emergency and accident procedures
- medical surveillance
- environment monitoring
- numbers of exposed workers
- employee training and education

This survey of Eli Lilly and Company in Indianapolis was conducted as one of a series of initial walk through surveys of firms utilizing recombinant DNA techniques in research or production processes.

DESCRIPTION OF THE FACILITY

Eli Lilly and Company, with multiple manufacturing sites in the United States and abroad, has its headquarters and many of its research and manufacturing operations in Indianapolis, Indiana. The company was founded in 1876 in downtown Indianapolis. Divisions of pharmaceuticals, agricultural products, cosmetics, electronic medical instruments, cardiac pacemakers, and research make up the corporate structure.

Eli Lilly's vast experience in the fermentation industry recently has been applied to the research and development of recombinant DNA technology. This is exemplified by the sophisticated equipment and systems used in Lilly's recombinant DNA processes. Eli Lilly is conducting its research and developing production under voluntary compliance with the National Institutes of Health (NIH) Guidelines for Recombinant DNA Research.

At the time of this survey, genetic engineering research was conducted in building 28, 731 S. Alabama St. and building 328, 1200 Kentucky Avenue. The main production development efforts are ongoing at the 1200 Kentucky Avenue location which houses various P-2, P-3, and P-1 containment level laboratories.

DESCRIPTION OF THE WORKPLACE

The Indianapolis facilities employ approximately 6,000 persons of whom about 4,200 are engaged in direct production of pharmaceutical products.

Since recombinant DNA fermentation is in the research/production development stage, very few employees are currently involved. The anticipated number of workers involved with recombinant DNA fermentation processes is expected to be minimal due to the nature of the process and the manpower requirements dictated by the system technology.

DESCRIPTION OF THE PROCESS

Fermentation processes, including those involving recombinant DNA, start in a P-2 or P-3 lab setting as ampoules of culture stored in N_2 which are then used to inoculate a shake flask containing the appropriate nutrients. After an incubation period the inoculum (the contents of a shake flask) is transferred, in a specially designed metal container, to the production floor. This container is designed to preclude escape or entry of viable organisms during inoculation of the fermentation vessel. Metal fermentation vessels used by Lilly for recombinant DNA range in sizes from 10-liters, 150-liters, or 2000-liters, depending upon the process, stage of development, or stage of culture growth. Culture is introduced into the 150-liter vessel or the 2000-liter vessel, by a stainless steel vessel that is sterilizable after transfer of the contents and before the vessel is detached from the fermentator, the vessels are charged with nutrients, water, and inoculum by closed system design to maintain physical containment.

The fermentation process is monitored and is terminated by chemical or physical means when the harvest stage is attained. Eli Lilly is currently using thermal techniques to terminate the process. The batch is then removed from the fermentor by pressure, and extraction of the desired product takes place. The mechanism of extraction may be by centrifugation or lysogenesis, depending upon the nature of the process and the desired product. Product extraction operations were not viewed during this visit.

The fermentor, inoculating device, shake flask and all exposed equipment are sterilized with steam after use to prevent contamination of succeeding operations and work environment.

DESCRIPTION OF INDUSTRIAL HYGIENE, SAFETY, AND MEDICAL PROGRAMS

Safety and Health

The company has a well organized safety and health program that is steered by the Corporate Safety and Health Committee and the Department of Industrial Health and Safety. Safety representatives are located at each site to monitor the work practices of employees. Periodic safety and housekeeping inspections are made in each plant by the plant safety representatives and a member of line supervision. Departmental and divisional safety committees, with rotating memberships, meet monthly for review of safety and/or health issues and to make recommendations.

The mayor of Indianapolis, a vice president of Indiana University (who is a physician), and a pathologist from Indiana University Medical School (an expert on infectious disease) are the non-company members of the IBC. The IBC reviews the work of the protocol review subcommittee (of the corporate safety and health committee) which is responsible for making containment recommendations for all recombinant DNA protocols, laboratories, production areas and procedures.

Work practice guidelines are maintained and available for specific procedures requiring personal protective equipment or precautions. Specialized safety equipment, laboratory coats, shoes, and glasses are provided by the company. Specific training programs for employees involved with recombinant DNA procedures have been instituted to instruct them in good work practices, process requirements, and emergency procedures. These include audio-visual presentations and instruction by supervisors. Communication meetings are held to discuss the status of recombinant DNA technology, the NIH Guidelines, and Lilly's advances in the field.

Industrial Hygiene

Environmental monitoring is limited to RODAC (Replicate Organism Direct Agar Contact) plates, air impaction onto agar plates, settling plates filled with agar, and liquid impinger techniques. Monitoring is performed on a scheduled basis during each run, and records are maintained. No viable recombinant organisms have been recovered. However, the sensitivity and accuracy of sampling and analytical techniques have not been documented for various culture and environmental conditions which may be encountered; the ability to recover viable culture organisms from contaminated surfaces or air has not been determined.

Medical Program

The company's medical department is staffed by a director of industrial medicine, five full-time physicians, and eight nurses who serve the employees in the Indianapolis area. Pre-employment physicals are given to newly hired employees. Comprehensive annual physicals are given to all employees and annual physical examinations are mandatory for all laboratory and production personnel (including recombinant DNA workers). Company policy states that all injuries must be reported to the plant physician and any employee on sick leave for more than five days must report to the physician before returning to work. Employees undergoing antibiotic therapy are excluded from working in recombinant DNA areas. Employees involved with recombinant DNA processes who develop chronic or acute illness are required to see the physician. Preassignment blood serum samples are maintained for individuals working with recombinant DNA processes. When appropriate, immunizations are given to those employees working with infectious organisms.

DESCRIPTION OF PAST EXPOSURES

Data on exposure of employees during fermentation processes with organisms containing recombinant DNA are limited to the results of the environmental monitoring previously mentioned and the medical surveillance program Eli Lilly has implemented. No quantitive data are available to document range or incidence of exposure. The company voiced concern about the practicability of the methods currently used for environmental monitoring, yet recognized the need for such monitoring.

EVALUATION OF THE PLANT AND PROGRAMS

Laboratory and Production Facility Design

Physical containment laboratories at the P-2 and P-3 level of containment used for research and development of recombinant DNA techniques were toured. These were well designed and were basically operated within the NIH Guidelines for Recombinant DNA research. A P-3 level laboratory utilized for research and shake flask fermentation was toured; no apparent problem areas were noted. A P-2 laboratory with 10-liter fermentors and bench-top continuous culture apparatus (being readied for operation) housed work concerning laboratory-to-production development.

The equipment specially designed for large scale growth of recombinant DNA organisms was housed in two locations. A room, separated by a partition from a conventional pilot fermentation area, housed modified 150-liter fermentors. A PI-LS (large scale) area with a 2000-liter fermentor, modified to contain recombinant DNA organisms will be used for production development and production of clinical trial material. This fermentation system was still in the developmental phase, and undergoing sterilization validation procedures, at the time of this survey; fermentation with recombinant DNA work is not housed in a distinctly confined room, but is in a pilot production area in immediate proximity to conventional fermentors of the same size. Access to the tops of the fermentors is by a single stairway and catwalk. Descriptions of fermentor modifications may be found in the following section and appendix 1 of this report.

Engineering Controls

As with other fermentation processes the concept of containment is not only to prohibit escape of organisms from, but also to exclude entry into the system. Thus, the engineering design and measures implemented by Eli Lilly to achieve the dual aspect of containment are quite sophisticated. This attention to process integrity and thus, effective control for personnel exposure demonstrates the level of containment that Eli Lilly attempts to maintain with recombinant DNA fermentation processes. Because of the design of this large scale operation, it is possible that more risk for worker exposure to recombinant DNA organisms (e.g. from accidental spillage or aerosol production) would occur in the shake flask laboratory than on the production floor.

The ventilation systems, exhaust gas filtration, waste products control, biological safety cabinets, barriers to unrestricted access, and all interior room surfaces in the P-3 and P-2 laboratories conformed to the NIH Guidelines. The NIH Guidelines for the P1-LS level does not require specific ventilation measures, or a distinctly confined area. Characteristics of fermentors used by Eli Lilly for organisms containing recombinant DNA molecules are:

1. Inoculation, sample collection, nutrient addition, and transfer of culture fluids can be performed with closed system piping. All pipes and feeder tubes are connected to a fermentor at its top.

2. Each fermentor has its own separate system of feeder lines, with the exception of electrical service, steam, and pH control (the latter two of which are double-check valved).

3. Agitator shafts which penetrate the fermentor shell have double mechanical seals and are top mounted on the fermentor.

4. The 150-liter fermentors are operated under slightly negative pressure, but the 2000-liter fermentors are operated at a slightly positive pressure (approximately 5 psi).

5. Sterilization of fermentor exhaust is accomplished by double filtration.

6. Drainage pipes at the bottom of fermentors are sealed closed.

7. Before initial use, the ability to sterilize an entire fermentor and its ancillary piping is verified by a test protocol employing thermocouples.

Validation Procedures

Validation of thorough sterilization of the fermentor, inoculation device, and exhaust gases is the responsibility of a validation team. A design engineer, two systems technicians, and the lead operator make up the team. Thermocouples and a recording system is utilized to assure that all points of the fermentor have been effectively sterilized. Each team member holds equal responsibility in giving approval for production start up of the fermentor. Thus, each must be confident that containment, sterilization, and inactivation procedures and systems are effective for size of the system, the specific host organism, and the recombinant DNA molecule.

The validation team also reviews the work procedures and practices of the operator during the fermentation cycle. Recommendations and changes in procedure can then be made by the team toward the prevention of breaching the containment design (resulting in exposure).

All biological safety cabinets undergo scheduled certification to demonstrate adequate performance. Autoclaves are also monitored for performance by use of recording charts. Centrifuge equipment received periodic maintenance checks to assure aerosol production is contained. Controlled access to the P-3 level laboratory is practiced and monitored by the laboratory supervisor. The laboratory ventilation systems are equipped with alarms that actuate in the event of a system malfunction.

Work Practices

No unsafe practices or poor laboratory techniques were noticed during this survey. The validation team line operators, supervisors, and the Corporate Safety and Health Committee monitor for poor personal hygiene habits and work practices. Adherence to safe work practices and company rules is required by the company. Maintenance of the fermentation systems and in the laboratories is performed only after lock out procedures have been implemented and approval granted from the line operators and the line supervisor.

Emergency and Accident Procedures

Plans for emergencies and laboratory accidents outline specific procedures for accidental spills in the laboratories. Corrective action for failure of equipment and/or facility safeguards are also included. Plans also exist for fire, explosion, and natural disaster. All of these plans are established and well known to those who work in the areas covered by the plans.

CONCLUSIONS

Experience has demonstrated that safe conduct of research and production processes involving potentially hazardous entities is dependent on good work practices, availability and use of effective control technology, and effective management. Advancement of recombinant DNA techniques into production processes is being undertaken at Eli Lilly in a responsible manner employing all of Eli Lilly's relevant expertise.

Evaluations of the product extraction process should be conducted once the company has developed the process to the point of utilization.

RECOMMENDATIONS

The P1-LS (2000-liter) production area should be segregated from other production operations by structural confinement. Additional containment controls could be implemented dependent upon future processes, host organisms, recombinant DNA molecules, and product of interest. This will maintain the integrity of the process and procedures outlined for recombinant DNA fermentation processes. Such system confinement will also enhance the containment of the entire operation to preclude accidental exposure to other employees and processes. This should be within the interests of good manufacturing procedures of the pharmaceutical industry.

A scheduled systematic preventive maintenance program for agitator seals, control valve, pressure release valves, and equipment/facility safeguards should be implemented. Possibly the validation team (with a maintenance representative) could manage such a program.

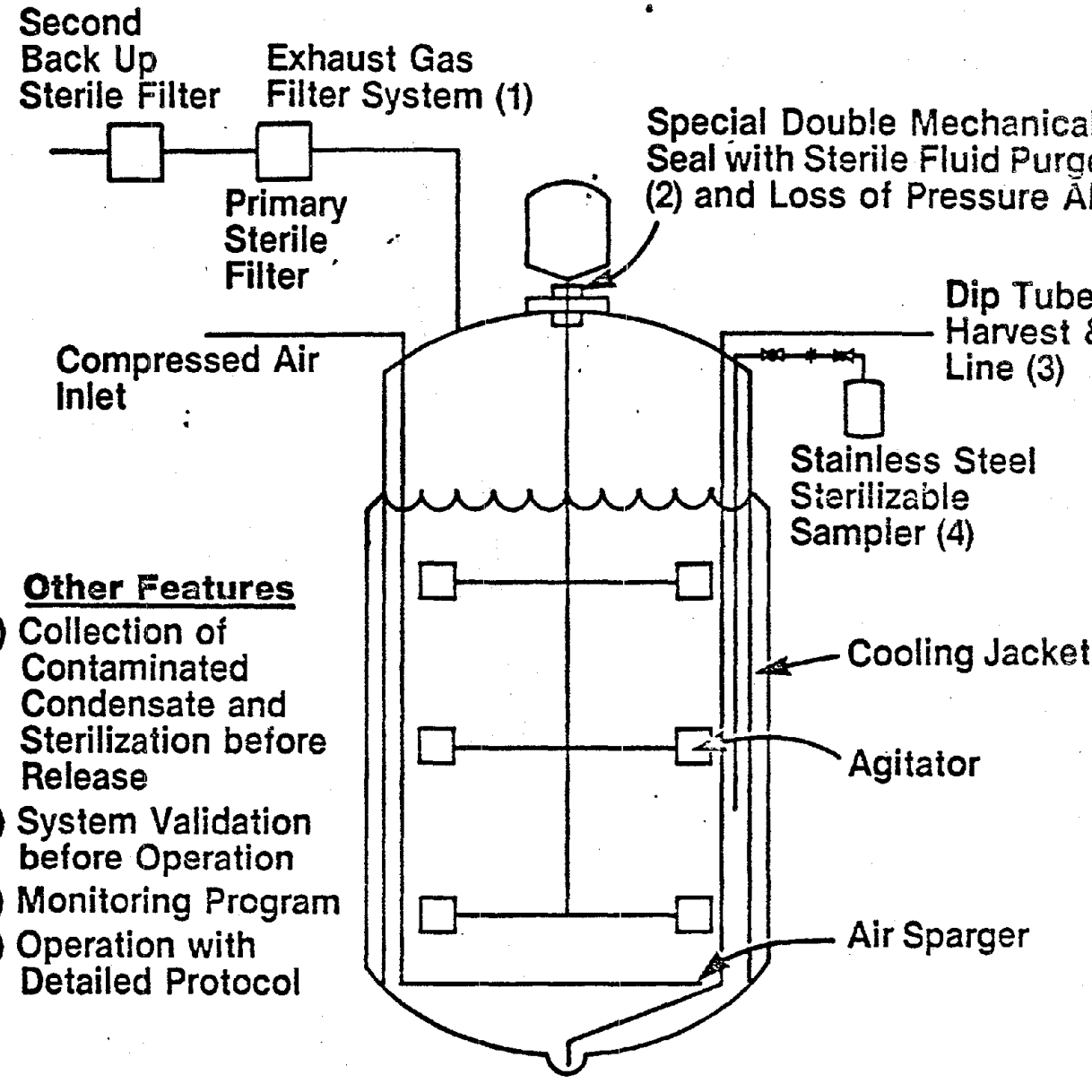
The efficacy, sensitivity, and accuracy of environmental sampling and analytical techniques should be investigated. A sampling protocol documenting procedures, analysis, sampling points, and sampling schedule requirements should also be devised.

An observation was made of a chemostat, with temporary tubing and fittings, sitting on an open laboratory table top in a P-2 laboratory. It is recommended that all chemostats, operating with recombinant DNA molecules or infectious organisms, be set up in class I biological safety cabinets or with secure leak proof tubing and fittings.

A registry of all owrkers employed with recombinant DNA processes should be established and maintained for reference to determine any abnormal medical problems or unusual occurances that someday may be attributed to recombinant DNA processes. NIOSH has had considerable experience in designing and maintaining such worker registries and can thus, provide assistance in design, implementation, and logistical requirements. The comparability of individual company registries is desirable for optimum and successful surveillance on an industry wide basis.

APPENDIX 1

Features of Contained Fermentor
Eli Lilly 2,000 Liter Fermentor



Other Features

(6) Collection of Contaminated Condensate and Sterilization before Release

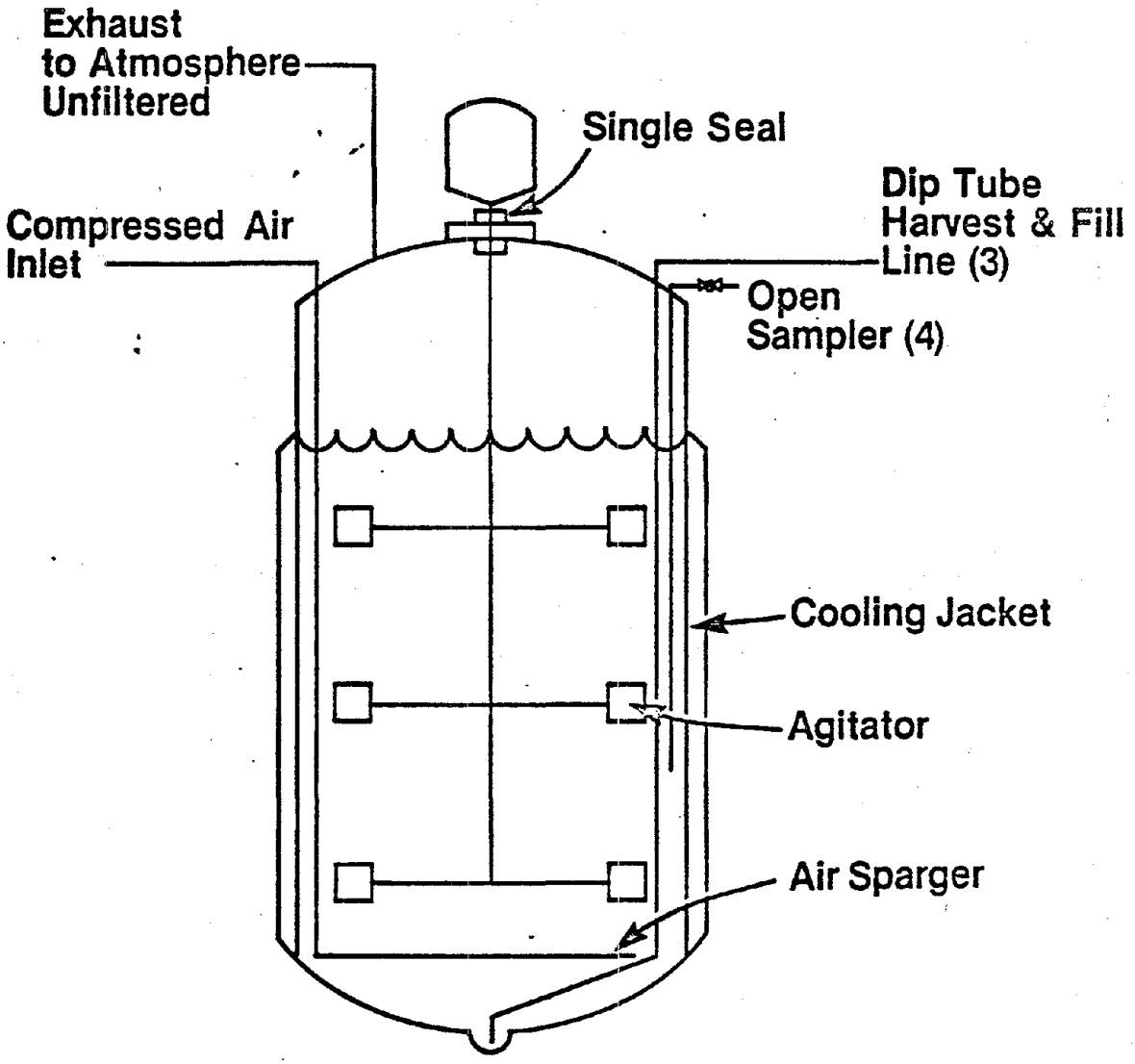
(7) System Validation before Operation

(8) Monitoring Program

(9) Operation with Detailed Protocol

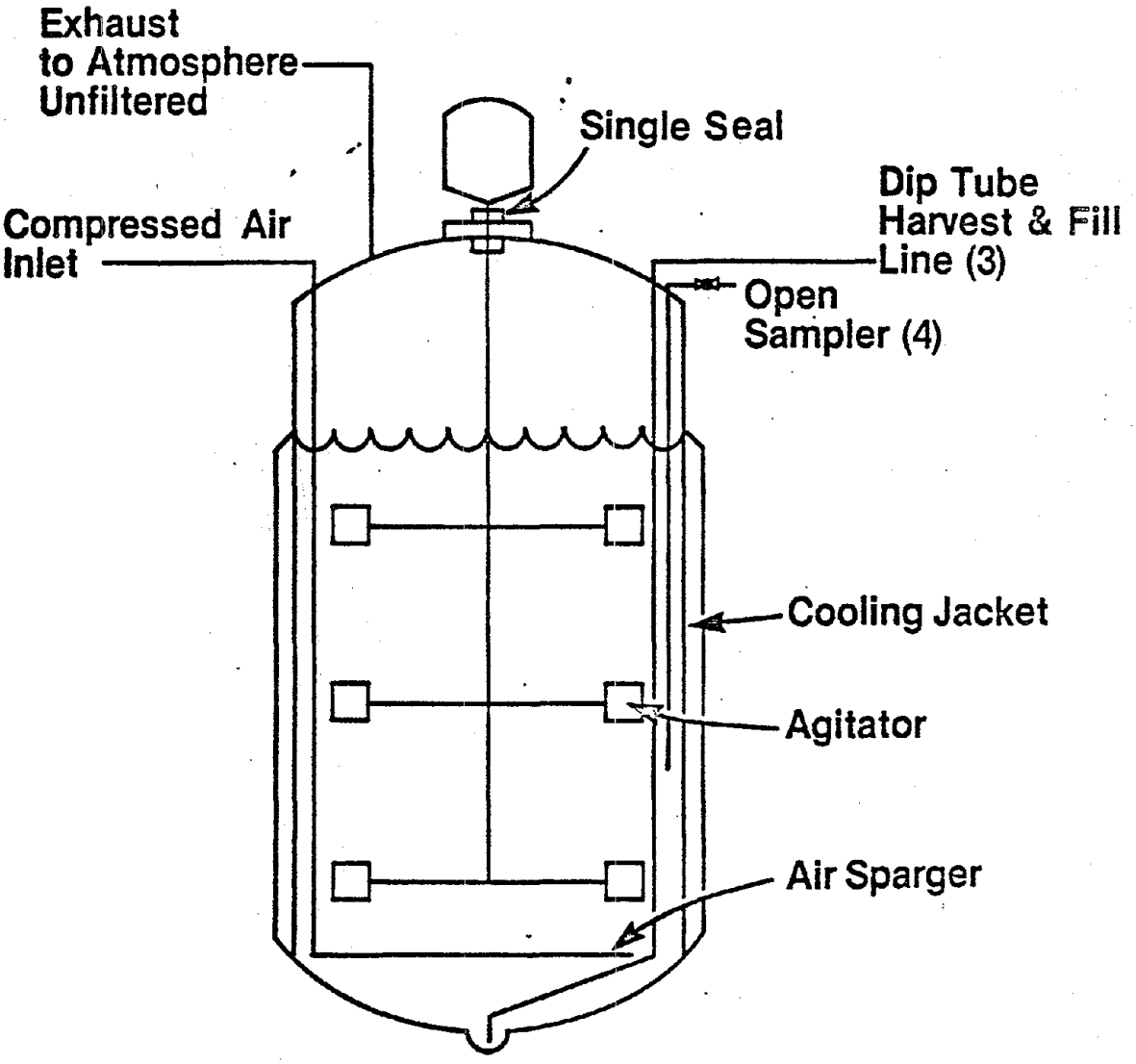
Submitted by the Eli Lilly Co.

Features of Standard Fermentor



Submitted by the Eli Lilly Co.

Features of Standard Fermentor



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