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THE PROJECT ENGINEERING ROLE IN RECOGNIZING TODAY'S ENVIRONMENTAL REQUIREMENTS AND THEIR IMPLEMENTATION

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Aerospace technology criteria leaped with both feet into the Pharmaceutical Industry ten or more years ago. This entry was given major impetuous by industry's desire to develop an improved technical basis for their environmental decisions (and most recently by increased FDA interest in this technology). At that time the Pharmaceutical Industry was, in most cases, ill equipped to handle many of the changes and implications associated with this technology, not the least of which was the actual criteria of design. This situation still exists at many corporations and is likely to remain until facts replace the all too often emotional judgments that presently establish environmental design criteria.

Environmental design, principally as it pertains to that branch of engineering referred to as "HVAC"; i.e. Heating, Ventilating, and Air Conditioning, has, to date, been given a high priority at our corporation as influencing almost all clean/aseptic (sterile) potential problems and, as such, our plant layouts and designs for our most critical environments are developed almost as much to suit air movements as production

requirements. Thus, the actual costs of our systems are not just in the HVAC systems and other design details, but also in the non-optimal production flow and techniques caused by our environmental concentration, as well as the costs associated with environmental monitoring. Despite these high costs per unit of production, we are unaware of data correlating actual environmental data to product quality which would allow establishment of environmental criteria based on a more technical and business basis. This situation, with increased emphasis on microbiological and particulate monitoring, is now rapidly being corrected.

This paper basically deals with a recently completed project and many of the environmental decision/implementation problems associated with that project. Finally, some recent data from that facility and a discussion of what that data may mean.

In early 1971, Abbott management approved funding for construction of an Ampoule and Vial Manufacturing facility in Rocky Mount, North Carolina, as an add-on to our existing I.V. Solution Manufacturing Facility. The facility incorporates distinct production lines broken down into the following categories:

Aseptic Liquid Filling Operations

Low Humidity Aseptic Powder Filling Operations

Clean (terminally sterilized) Liquid Filling Operations

Powder Fill Operation

Although the design problem was one of an "aseptic" as well as a low particulate approach after a search within the time available, it was concluded that there were no published standards pertaining to permissable levels of viables in aseptic installations.

It was concluded, however, that although there was no definitive relationship available between particulate and viable counts, that a low particulate count could be expected to provide an acceptable environment for aseptic filling.

Basic particulate criteria were then established for the fill line as follows:

	GENERAL ROOM FILTRATION	CLASS 100 AIR OVER PRODUCT	RELATIVE HUMIDITY	RELATIVE PRESSURE
Aseptic Liquid Fill	HEPA-Terminal	HEPA Filters, Curtains	35-55% RH	+++
Aseptic Powder Fill	"	"	15-22% RH	--
Clean Liquid Fill (T.S.)	"	"	35-55% RH	+

The basic air flow design concepts as shown in FIGURES I thru III were:

FIG. I indicates the basic pressure relationships and air flow direction for aseptic fill areas. Rather than attempting to control to a specific pressure-by-pressure control technique, we attempt to keep the air flow direction from clean to less clean areas, realizing that temperature gradients and opening of doors temporarily interrupt these relationships. Such devices as the mechanical flow simulator and smoke testing have been effectively used for this task.

FIG. II (Typical Aseptic Fill Room) pictorially describes some of those concepts Abbott considers desirable for an aseptic facility such as:

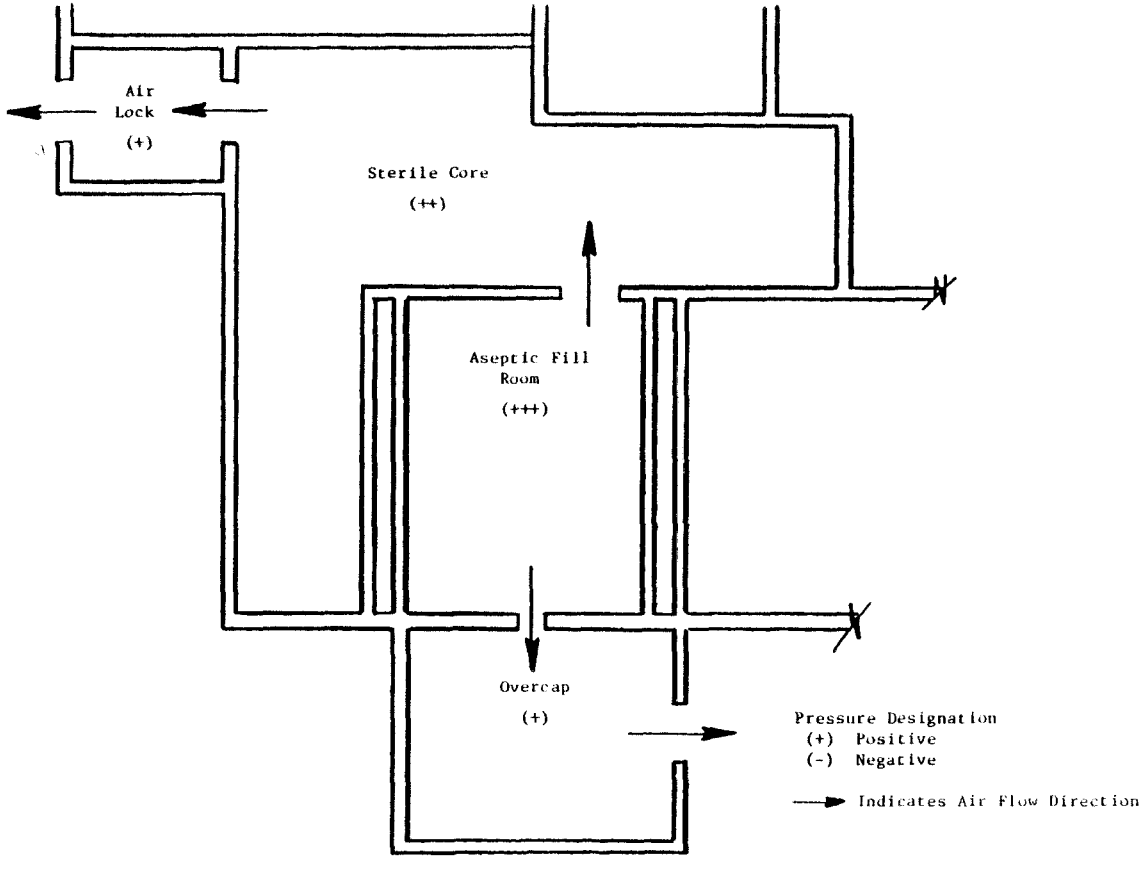


FIGURE 1. Typical Pressure Relationships for Aseptic Fill Area.

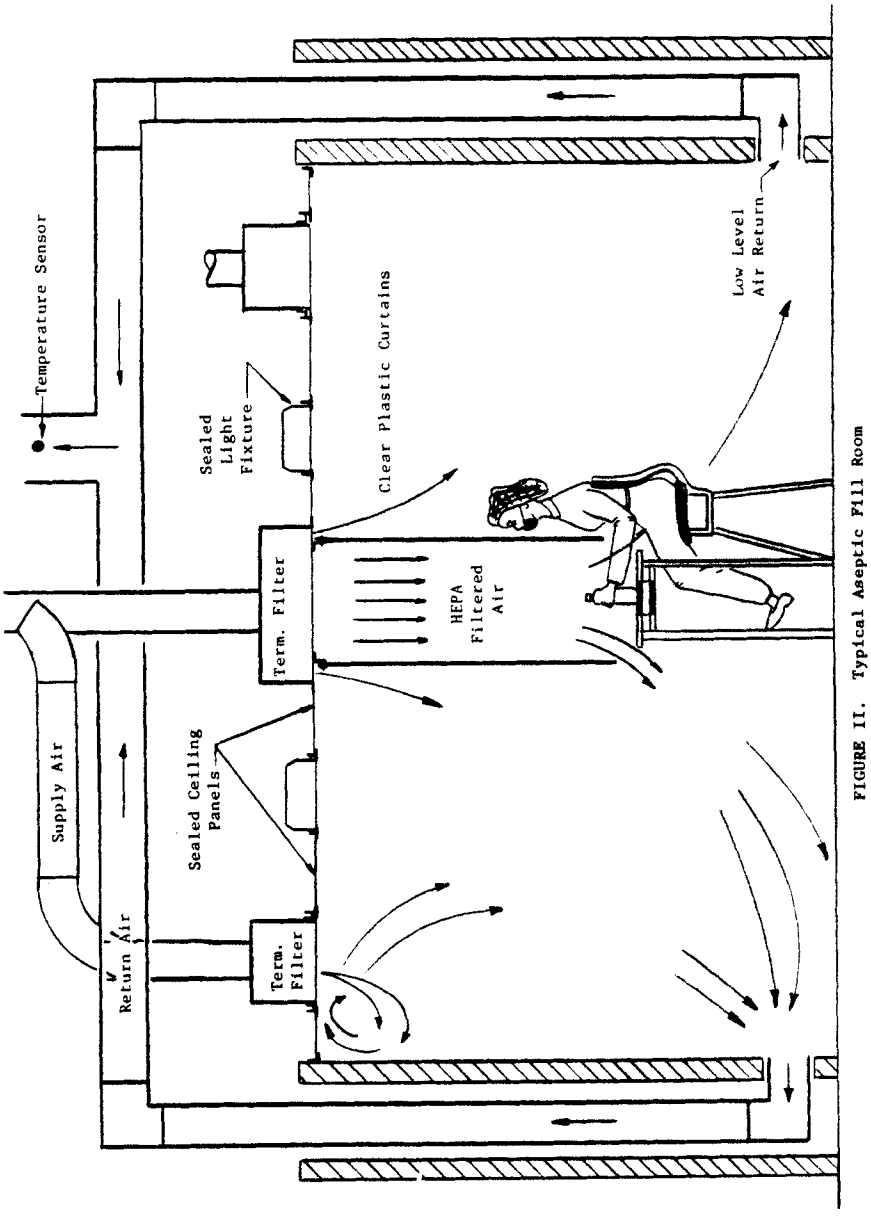


FIGURE II. Typical Aseptic Fill Room

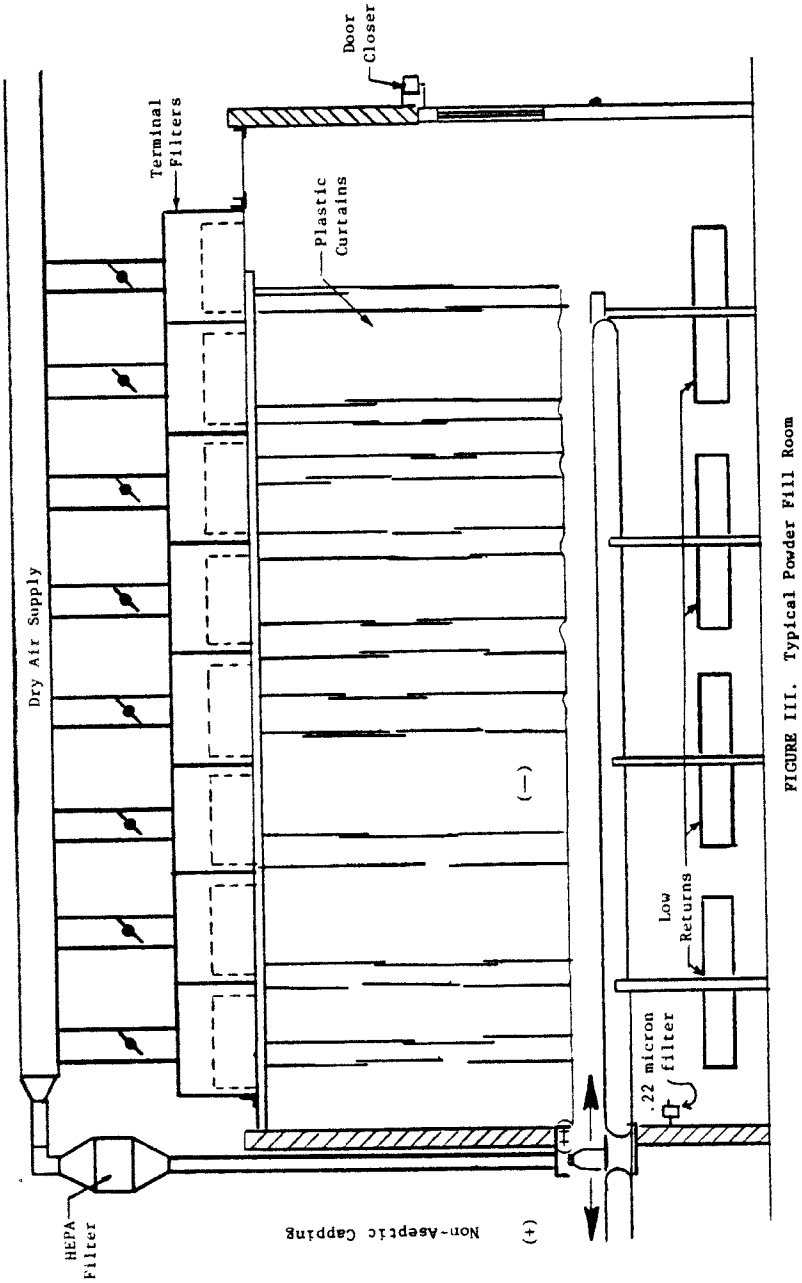


FIGURE III. Typical Powder Fill Room

1) Low returns to "sweep" the floor and control air direction.

2) Product protection (by the use of plastic curtains) rather than entire room protection.

3) Terminal HEPA filters rather than HEPA filters at the air handler discharge.

4) Sealed ceilings as well as sealed light fixtures.

Along with some additional concept details shown in FIGURE III (door closers on least clean side, .22 micron filters on all air/gases brought into the room), a product pressure plenum concept was developed for this negative pressure powder fill room in order to prevent air flow from the non-aseptic capping area into the aseptic powder fill room.

In order to control the environmental construction aspects of these rooms and thus the final product, the following program was implemented:

A. Initial conceptual design in house, final design carried out by an outside A-E firm with monitoring by the Abbott staff.

B. Equipment purchased by Abbott:

1. All clean/sterile area air handlers.

2. Terminal and after filters, installed and tested.

C. Separate contracts by Abbott:

1. HVAC
2. Mechanical Piping
3. Filters (Hoods, filters, filter installation, DOP testing, and certification).
4. Controls
5. Test and Balance
6. Above ceiling cleanup

In the case of separate contracts, prior to lump sum bidding, all contractors were called in to discuss the project prior to their submission of proposals--in the HVAC and Mechanical cases, the project engineer and the HVAC engineer visited the contractor's shops for approximately 1/2 day each, with 90+% complete drawings in order to obtain a knowledge of the contractors' capabilities, as well as truely competative bids. In addition, all changes to contracts (field or design) were controlled and administered by the Abbott project or site engineer.

Despite these precautions, and as with any complex construction, temporary problems occurred, such as:

A. Air Handler fan vortex controls were mispurchased by the fan supplier, had to be changed out in the field.

B. Powder room ductwork was not provided according to spec (welded aluminum)--partially replaced in field.

C. Air handlers not properly bolted to the floor.

D. Fire Damper installation not according to SMACNA (Sheet Metal and Air Conditioning National Association) requirements and many were missing. Re-installed and additional units purchased.

E. Volume damper construction did not meet SMACNA requirements for the thru rod construction with excessive widths.

F. Ductwork intermediate bracing did not meet SMACNA requirements for large ductwork sizes.

G. Filter contractor did not want to field DOP test his filters, although in specification, eventually did same.

H. Control panels, supposedly factory checked, required some field rewiring.

I. Volume dampers in certain large HEPA filter hoods which would not stay in a fixed position (other than fully closed).

J. Dryers would not perform.

The first production line started up approximately on schedule and subsequent line startups spaced, on the average, well over a month apart, have subsequently been placed into production.

Environmental tests are performed on a routine basis and data of actual findings during the period from March thru July 1974 are shown in Figs. 4 and 5. After line startup, the monitoring function became a quality assurance responsibility and the

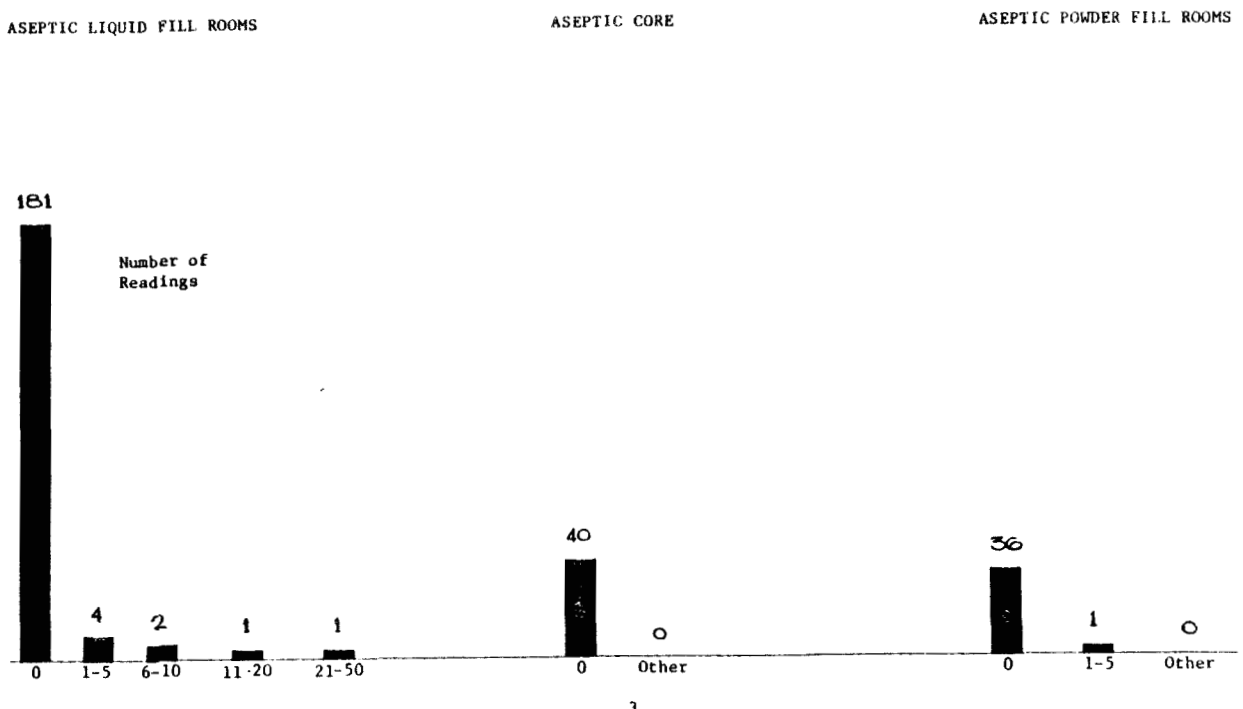
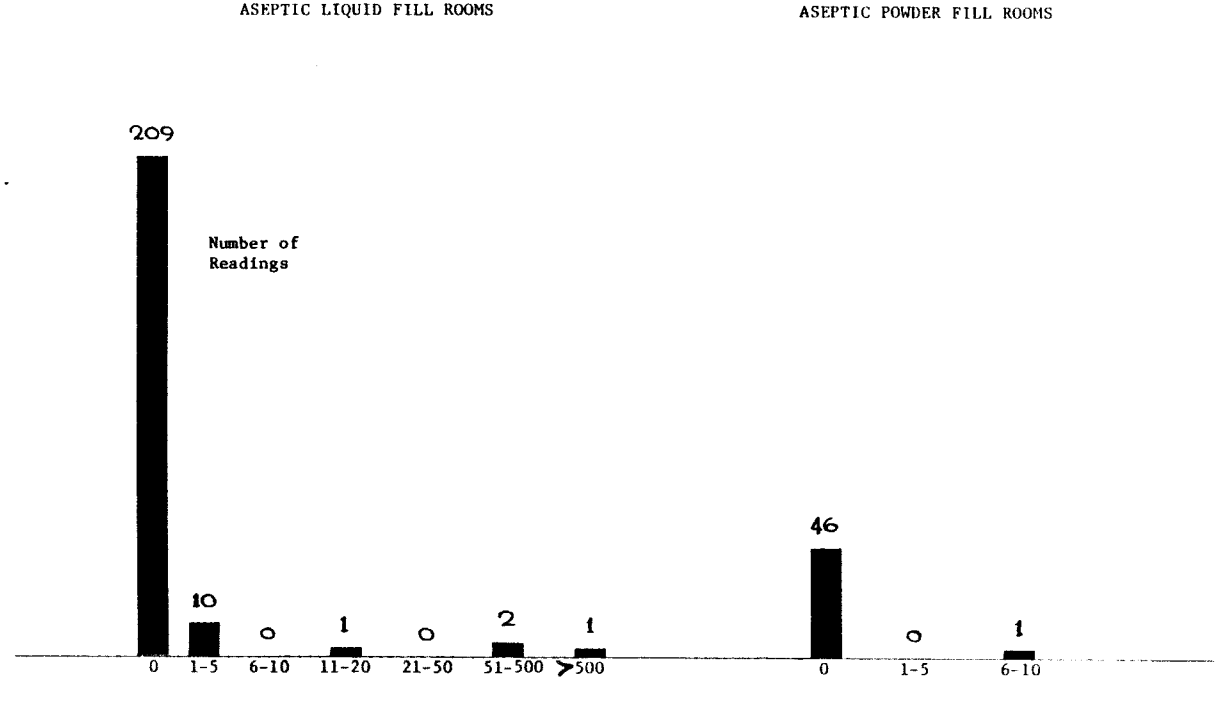


FIGURE IV

March-July 1974



VIABLES ON CONVEYOR/TURNTABLE (IN VIABLES PER 25 CM^2)

FIGURE V

March-July 1974

actual measurements have been based on viables (actual live bacteria) per volume of air or surface area rather than the particulate level approach which served as the design basis. The monitoring is principally done on a microbiological basis rather than a particulate basis in that our major concern for these systems is microbiological with particulate levels being secondarily significant. Importance of the final product quality being more a function of washing quality rather than air quality.

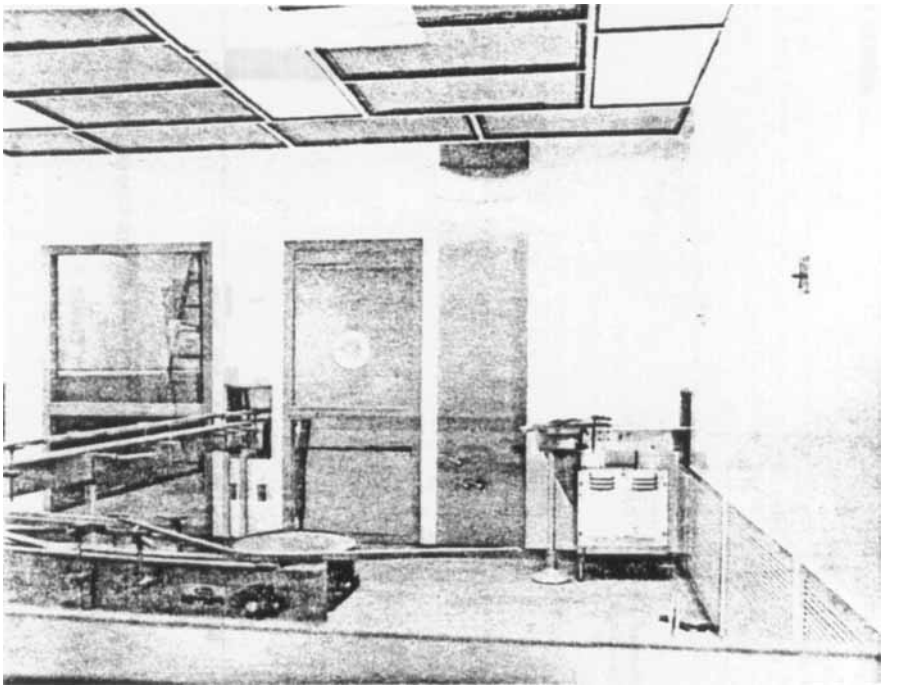


FIGURE VI

Fig. VI describes the actual viables level in aseptic fill rooms (per 30 ft^2), as obtained by a slit air sampler. The samples were taken on a daily basis while actual filling was taking place, and only for those rooms in production.

Fig. VII indicates results of swab samples on work surfaces (conveyors or turntables) under curtained laminar flow while production was also in progress.

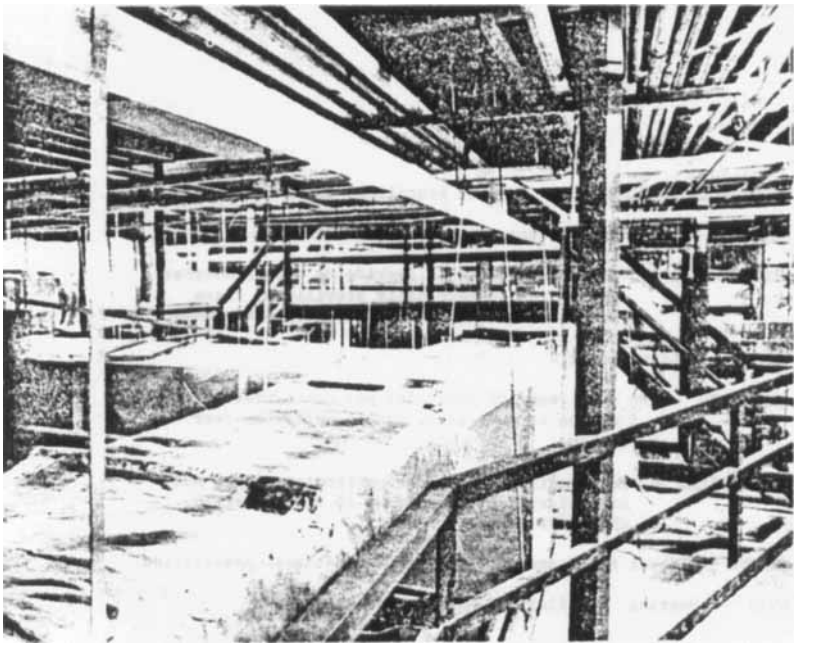


FIGURE VII

Where viable counts have peaked, these have been of short duration, as subsequent "follow-up" tests taken have been at the "zero" level proving to our satisfaction that the air systems are "cleaning up" locally generated viables.

We believe Abbott is satisfied with the performance of their systems. It is anticipated that future data will allow us to fine tune our design so the desired results can be achieved more economically.

DEFINITIONS

1) TERMINALLY STERILIZED - Product sterilized after filling.

2) ASEPTIC - Free from living organisms, sterile.

3) ASEPTIC FILL - Some products would degrade or have a shorter shelf life if terminally sterilized, these products are filled in an aseptic environment.

4) VIABLE - Live bacteria.

5) CLASS 100 - No more than 100 particles per cubic feet of .5 micron or more size, and no particles over 5 micron.

6) DOP TESTING - Introduction of a known particulate level and size distribution upstream of the filter to check for leaks.

7) SMACNA - Sheet Metal and Air Conditioning National Association.

8) HVAC - Heating, Ventilating, and Air Conditioning.