IN-DEPTH SURVEY REPORT:

CONTROL TECHNOLOGY ASSESSMENT OF UNIT OPERATIONS EMPLOYED IN ORAL CONTRACEPTIVE TABLET MAKING OPERATIONS

AT

Ortho Pharmaceutical Corporation
Raritan, New Jersey

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Division of Physical Sciences and Engineering
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INTRODUCTION AND SUMMARY

The Occupational Safety and Health Act of 1970 (PL 91-596) was enacted to "assure safe and healthful working conditions for men and women." The Act established the National Institute for Occupational Safety and Health (NIOSH), which is now in the Department of Health and Human Services. NIOSH was charged by this Act to conduct research and develop criteria for preventing exposure of workers to harmful chemical and physical agents. In response to this legislative mandate, NIOSH has conducted major programs to document, develop, and disseminate information regarding the recognition, evaluation, and control of such agents.

In 1976, NIOSH instituted a major effort to prevent occupational health problems through the assessment and application of control technology in the workplace. This control technology research program involves engineering assessments in which effective options for the solution to employee exposure problems are evaluated and documented. The major goals of the assessment program are to establish a catalogue of solutions by documenting successful applications of control measures, and to foster the more widespread application of these solutions through technology transfer.

Oral contraceptives (OC) have been selected for study because they represent the largest single use of estrogens, and because they are processed using rather typical pharmaceutical technology. From a control technology point of view, the biological potency of these materials has led manufacturers to implement rigorous control systems. The unit processes employed in manufacturing (preweighing of actives and excipients, mixing and granulation, tableting, and packaging) are common within the pharmaceutical industry. A systematic characterization of the controls used in OC tablet manufacturing is therefore beneficial in batch manufacturing processes wherein similar unit operations and active ingredients of similar potency are employed, both within and outside of the OC processing operations.

In the late 1970's, Ortho Pharmaceutical Corporation (OPC) designed and built a new plant including a processing facility for the manufacture of OC

tablets. The process includes facilities for 1) preweighing of active ingredients, 2) wet mixing of active ingredients and excipients and drying to produce a granulation (processing), 3) compression of the granulation into tablets (tableting), and 4) packaging.

This report documents the concepts and principles underlying the health hazard controls associated with the manufacturing operations.

PRODUCTS AND PROCESSING OPERATIONS

PRODUCTS

OPC manufactures several types of unit dose OC tablets at the Raritan facility. Ortho-Novum(R) tablets contain 1 milligram norethindrone (NOR), but their potency with respect to mestranol (MES) varies. Ortho-Novum(R) 1/35, 1/50, and 1/80 contain 35, 50, and 80 micrograms of mestranol respectively. Also produced are Modicon(R) tablets which contain 35 micrograms of ethynylestradiol (EE) and 500 micrograms of norethindrone. The production schedule during the NIOSH survey is given in Table 1.

Table 1. OC Production Schedule During NIOSH Survey

			Packaging	
Date	Processing	Tableting	T-line	V-line
6/13/83	-	1/80	1/50	1/35
6/14/83	1/35	1/80	-	1/35
6/15/83	1/35	-	-	1/35
6/16/83	-	Modicon	1/50	-
6/17/83	-	Modicon	1/50	-

FACILITY LAYOUT

A plan view of the OC manufacturing facility is given in Figure 1. Access to the high risk areas [preweighing (P-415), processing (P-423), and tableting (P-429)] is through an entrance door adjacent to the men's locker room (P-418) after appropriate personal protective equipment (PPE) has been donned. Egress from these high risk areas is through the water shower and back to the men's locker room. Excipients are brought to the Material Staging Room (P-416) while actives are handled in the Preweigh Room (P-415).

There are two packaging lines - the T-line (P-406) and the V-line (P-406A).

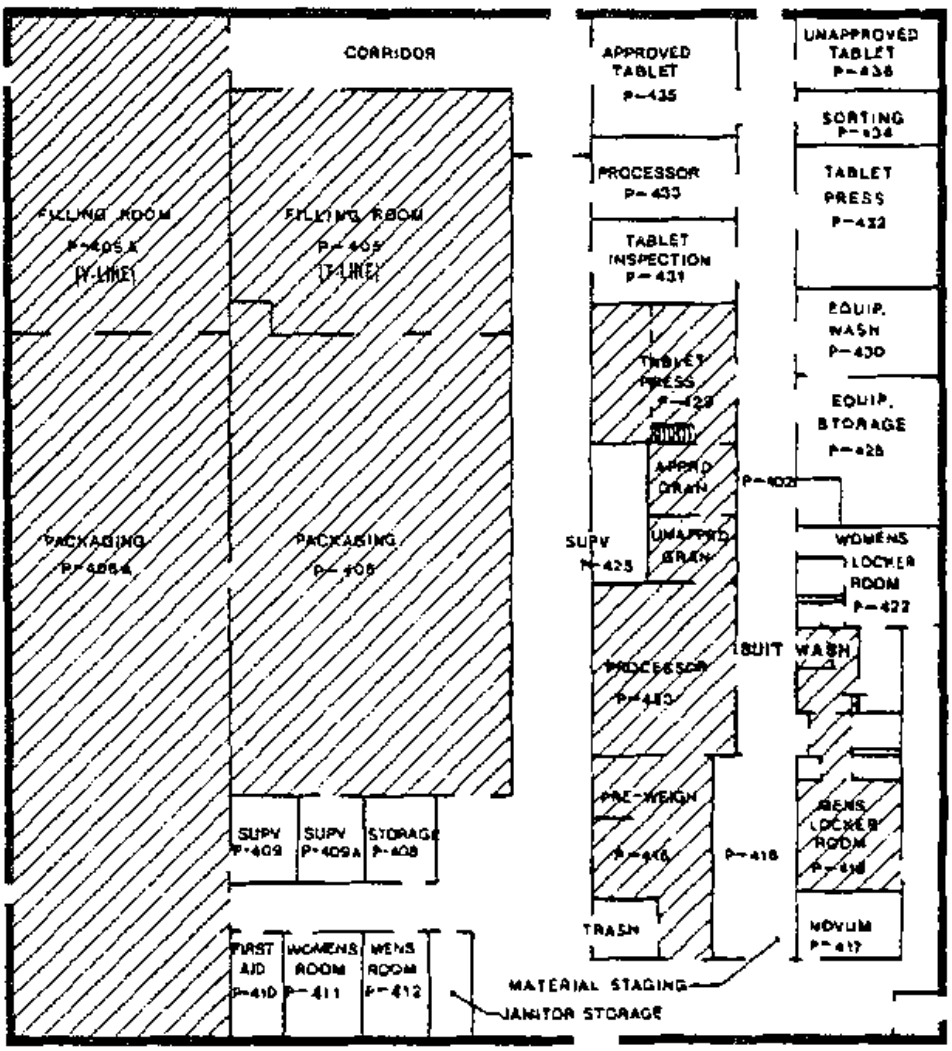

Figure 1. Plan View of Ortho Pharmaceutical Novum Complex

Note: Shaded Areas Were Active During NIOSH Survey

PREWEIGHING OF INGREDIENTS

Active ingredients are weighed in the preweigh room. Rather than weighing out ingredients one batch at a time, ingredients for many batches are weighed out according to the projected schedule of production. One worker weighs the batches using an electronic balance located in a hood (to be described later). The material for each batch is placed in a container lined with a clear plastic bag.

Excipients constitute more than 99 percent by weight of the batch. They are preweighed into fiber drums at a location outside the steroid manufacturing facility and are brought to the Material Staging Room.

PROCESSING (GRANULATION)

Excipients in the Material Staging Room are transferred from drums to the V-Blender by use of a VAC-U-MAX(R) system (VAC-U-MAX Corporation). A schematic of the system is shown in Figure 2. When transferring powder from the drum to the V-Blender, vacuum is developed by the vacuum pump and powder mixed with air moves through the lines to the blender. The small amount of powder that does not settle in the blender is intercepted by the canvas filter. As more powder deposits on the filter, it becomes plugged - thus inhibiting airflow. In this case, "blowback" of the filter is necessary. This is accomplished automatically by closing the pinch valve and turning the four-way valve such that outside air flows toward the filter housing. The flow is induced by the vacuum which existed during the first part of the cycle. The sequence (blowback and material flow) is controlled by a timer. To protect the vacuum pump from being deadheaded during blowback, the safety valve opens when a preset vacuum level is reached in the suction side of the pump.

Norethindrone is added to the V-Blender directly. MES or EE is dissolved in a preweighed quantity of solution in a small mixing tank. The EE or MES container is rinsed with solution. A positive displacement pump is used to transfer the solution of active to the V-Blender.

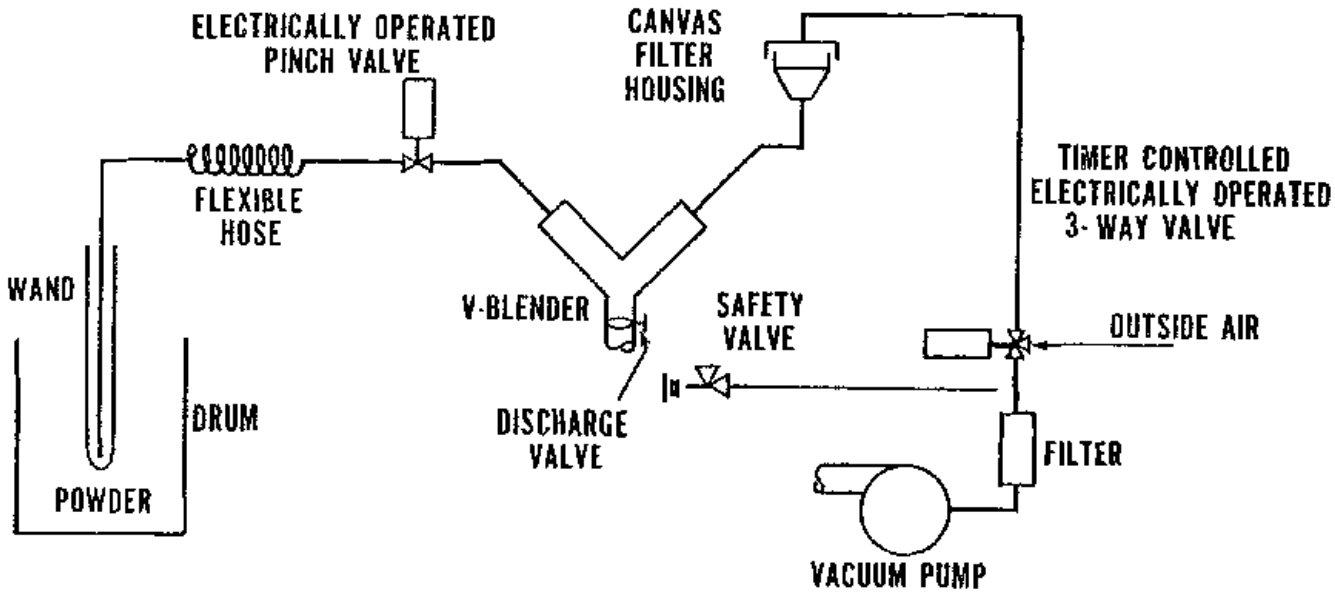

Figure 2. Schematic of Vac-U-Max(R) Transfer System

The mixing and drying scheme for production of granulation used at OPC is shown in Figure 3. The solution of actives MES or EE is dispersed through other ingredients by pumping under pressure through the "intensifier bar" of the V-Blender while the latter is rotating. The liquids in the wet granulation are removed by passing steam-heated fluid through the V-Blender jacket. The vapor produced is withdrawn by vacuum (pump) and is condensed in two condensers in series as shown in Figure 3. Chilled water is passed through the condenser jackets. The worker uses a "thief" to sample granulation from both sides of the blender when drying is complete. A loss-on-drying test is performed on these samples. After it has been determined that drying is complete, a "capsule" is rolled underneath the blender to receive all of its contents. The capsule is attached to the V-Blender before the dump valve is opened, making it essentially a closed system.

One worker operates the system during the shift. However, help from one or two additional workers is required at the beginning when transferring excipients and actives to appropriate pieces of equipment and at the end when emptying the V-Blender contents into the capsule. In the latter instance, a worker on top of the blender uses a tool to push residual granulation into the capsule.

TABLETING

The tableting operation is performed in a room dedicated for this purpose. One worker operates the tableting machine and performs quality control testing which includes the periodic monitoring of tablet weight and friability.

The tableting machine used at the OPC facility is a Manesty rotapress MK IIA sold in the U.S. by Thomas Engineering, Hoffman Estates, Illinois. The machine and associated equipment are shown schematically in Figure 4. Granulation is fed to the rotary press from a capsule that is inverted over the feed chute which terminates into a flange at floor level in the mezzanine. Figure 5 is a photograph of the capsule in place. Granulation in the chute is fed to the two machine hoppers by screw conveyors. A force-flow

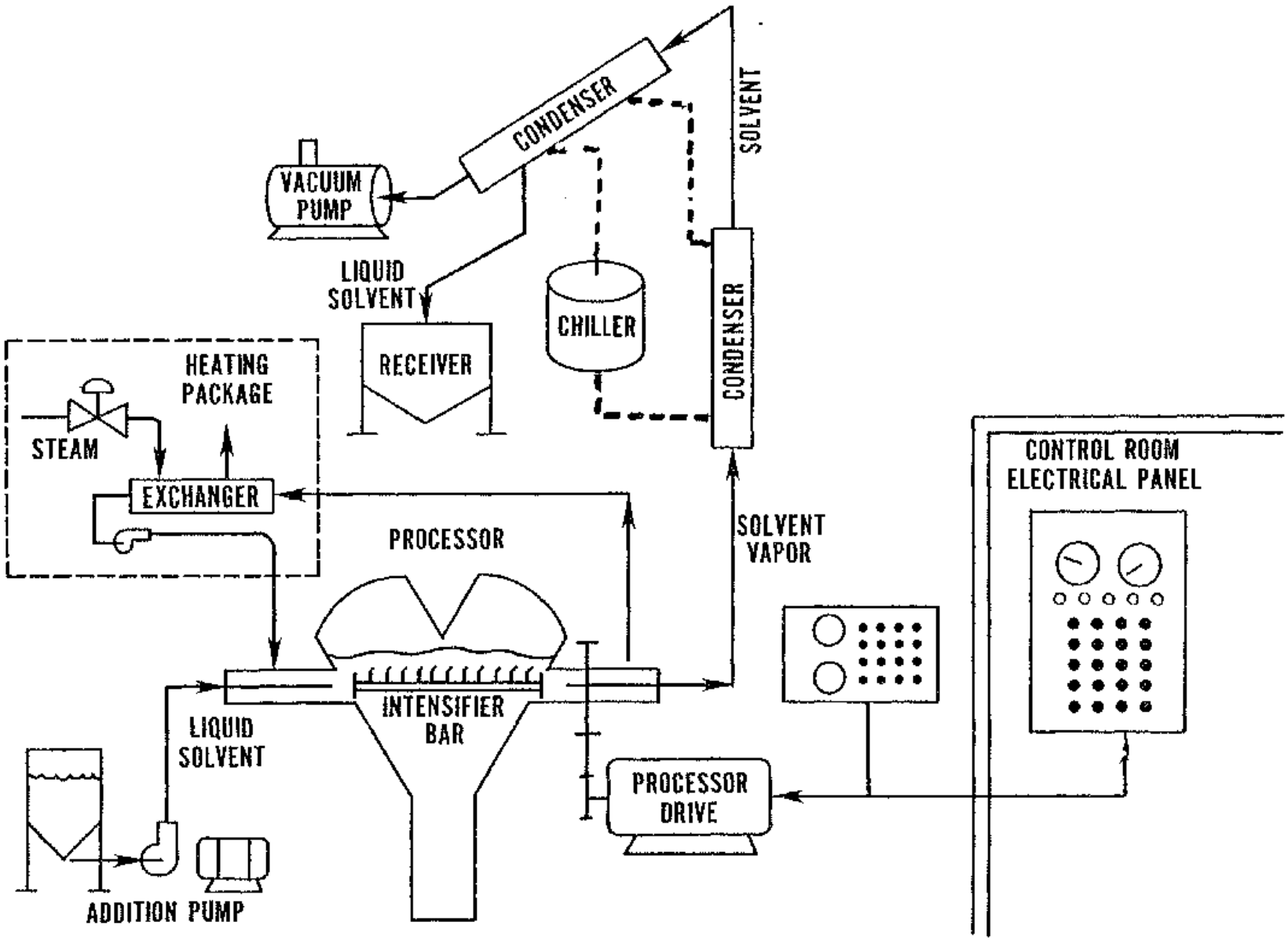

Figure 3. Granulation Production Schematic Process Flow Diagram

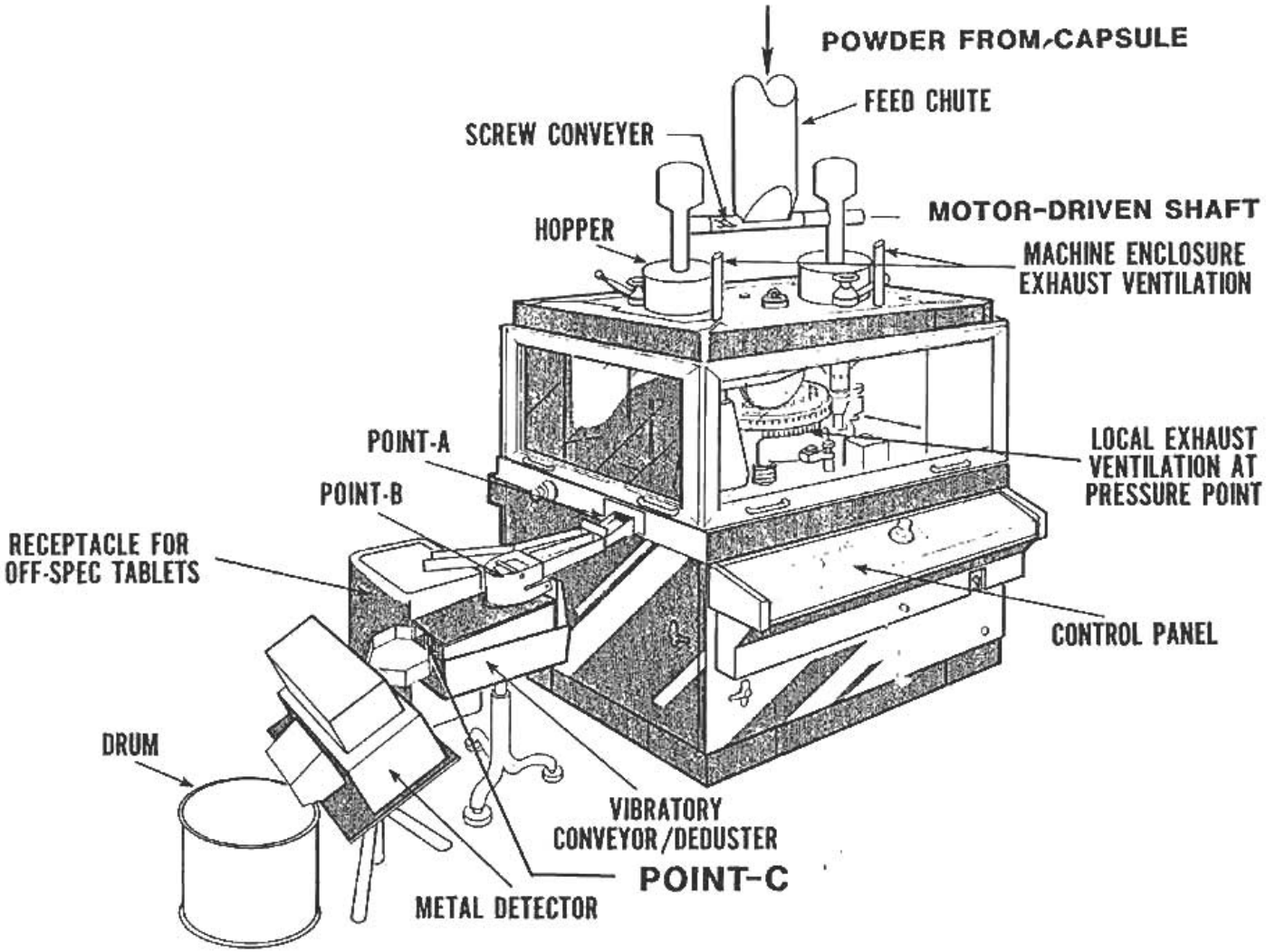

Figure 4. Tableting Machine and Associated Equipment

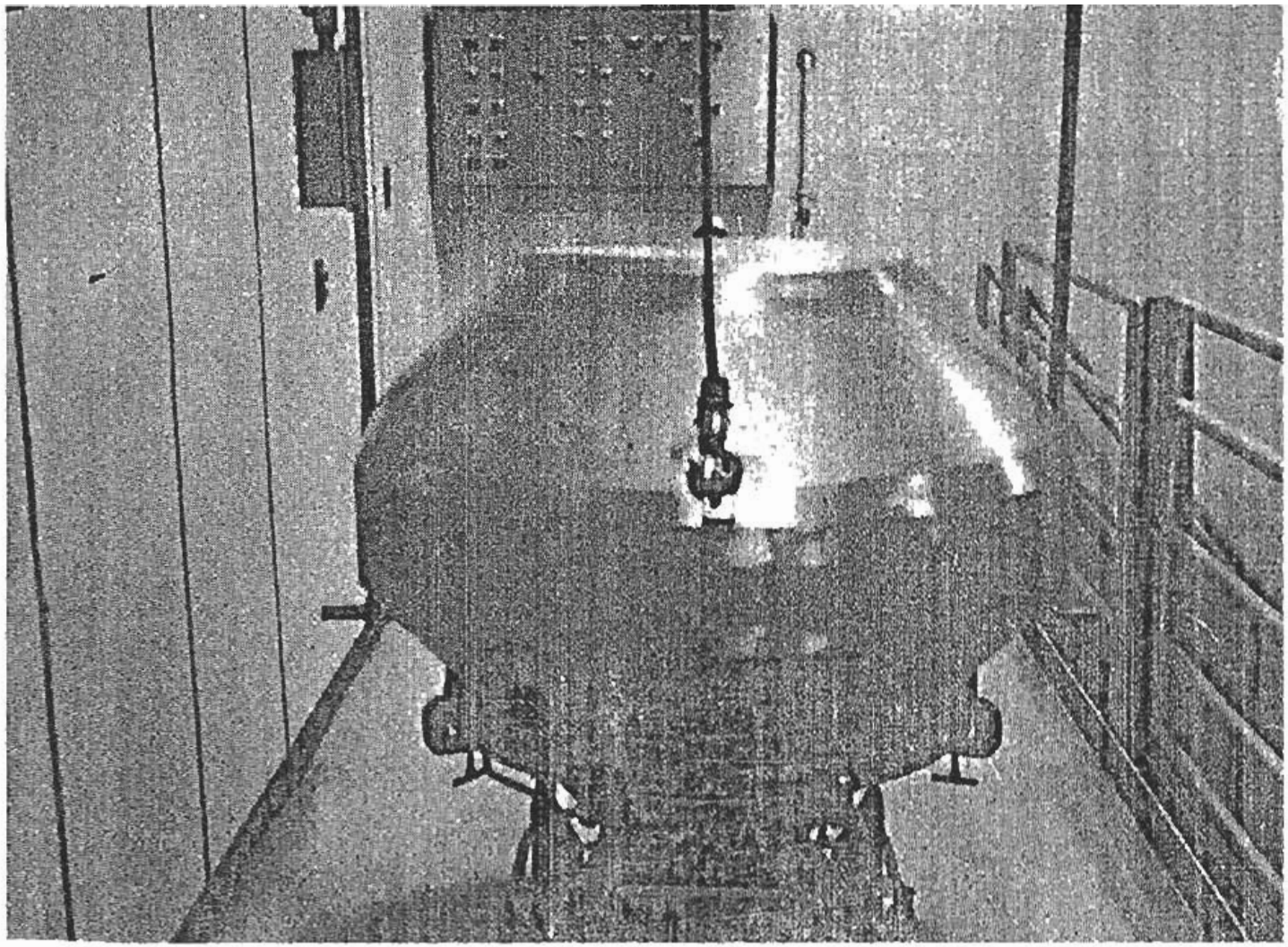

Figure 5. Capsule Containing Granulation

feeder (shown in Figure 6) accomplishes feeding of the dies and scraping of excess powder. From this point on, the machine is similar in operation to other rotary machines whose principle of operation is shown in Figure 7 and explained below.

The pull-down cam (C) guides the lower punches to the bottom of their vertical travel, allowing the dies to overfill. The punches then pass over a weight-control cam (E), which reduces the fill in the dies to the desired amount. A blade on the larger of the two star-shaped rotors fills the die and another blade removes excess granulation. Next, the lower punches travel to the lower compression roll (F) while simultaneously the upper punches ride beneath the upper compression roll (G). The upper punches enter a fixed (usually) distance into the dies, while the lower punches are raised to squeeze and compact the granulation within the dies. To regulate the upward movement of the lower punches, the height of the lower pressure roll is adjusted. After the moment of compression, the upper punches are withdrawn as they follow the upper raising cam (H); the lower punches ride up the cam (I), which brings the tablets flush with or slightly above the surface of the dies. The exact position is determined by a threaded bolt called the ejector knob (J). The tablets strike a sweep-off blade and slide down a chute into a hopper which feeds a vibratory conveyor. At the same time, the lower punches re-enter the pull-down cam (C) and the cycle repeats.[5]

PACKAGING

The OC tablets obtained from the tableting operation are packaged, along with placebo tablets, in circular packs. The machinery which produces the circular packs is proprietary. The discussion of the packaging process will, therefore, be general in nature.

The packaging room at OPC is physically divided into two parts. The first part (filling) is physically separated and environmentally isolated from the second by a wall with two doors, one on each side of the conveyor. The latter passes through a window to the second part of the room (called packaging).

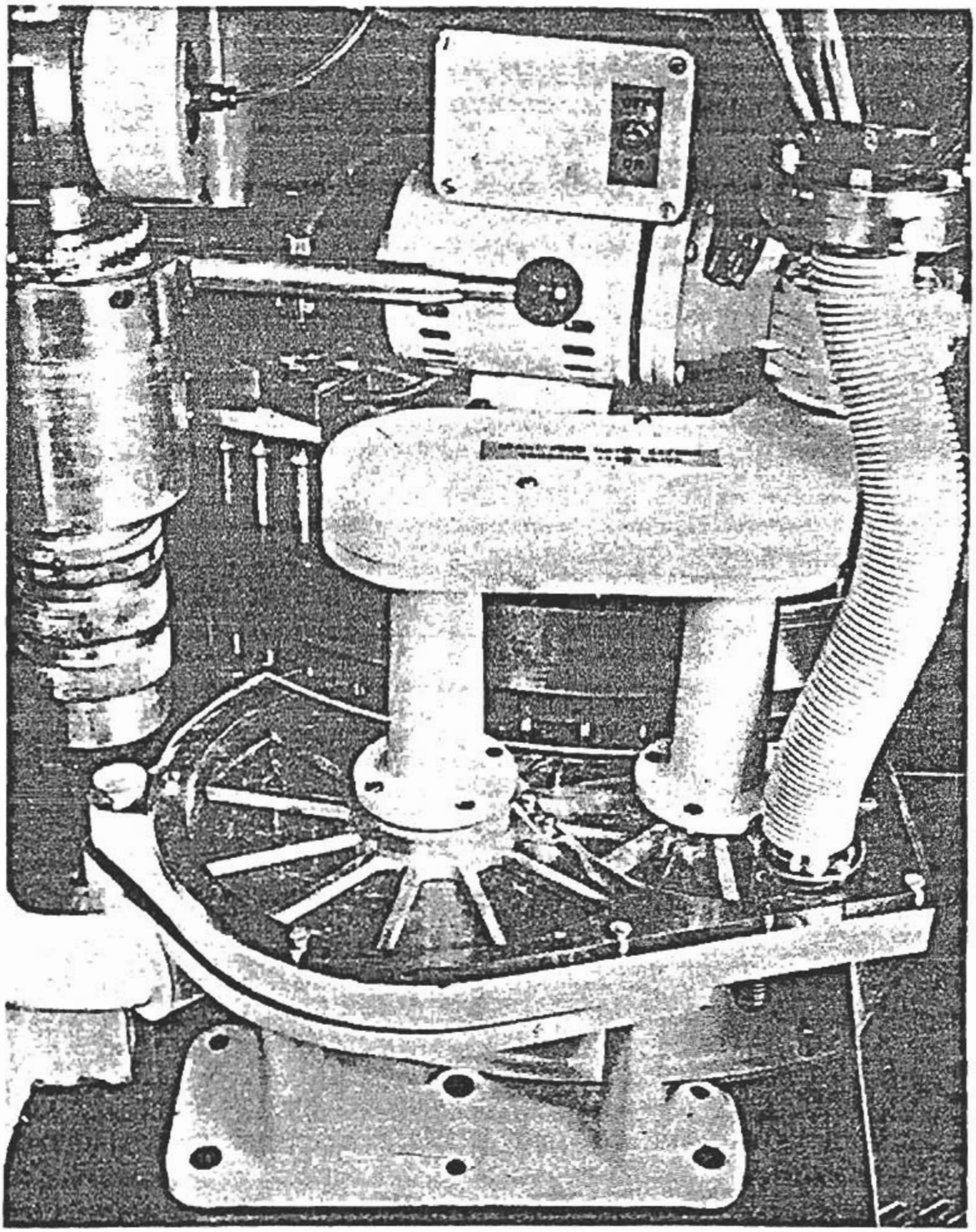

Figure 6. Manesty Force Flow Feeder (Ref. 1)

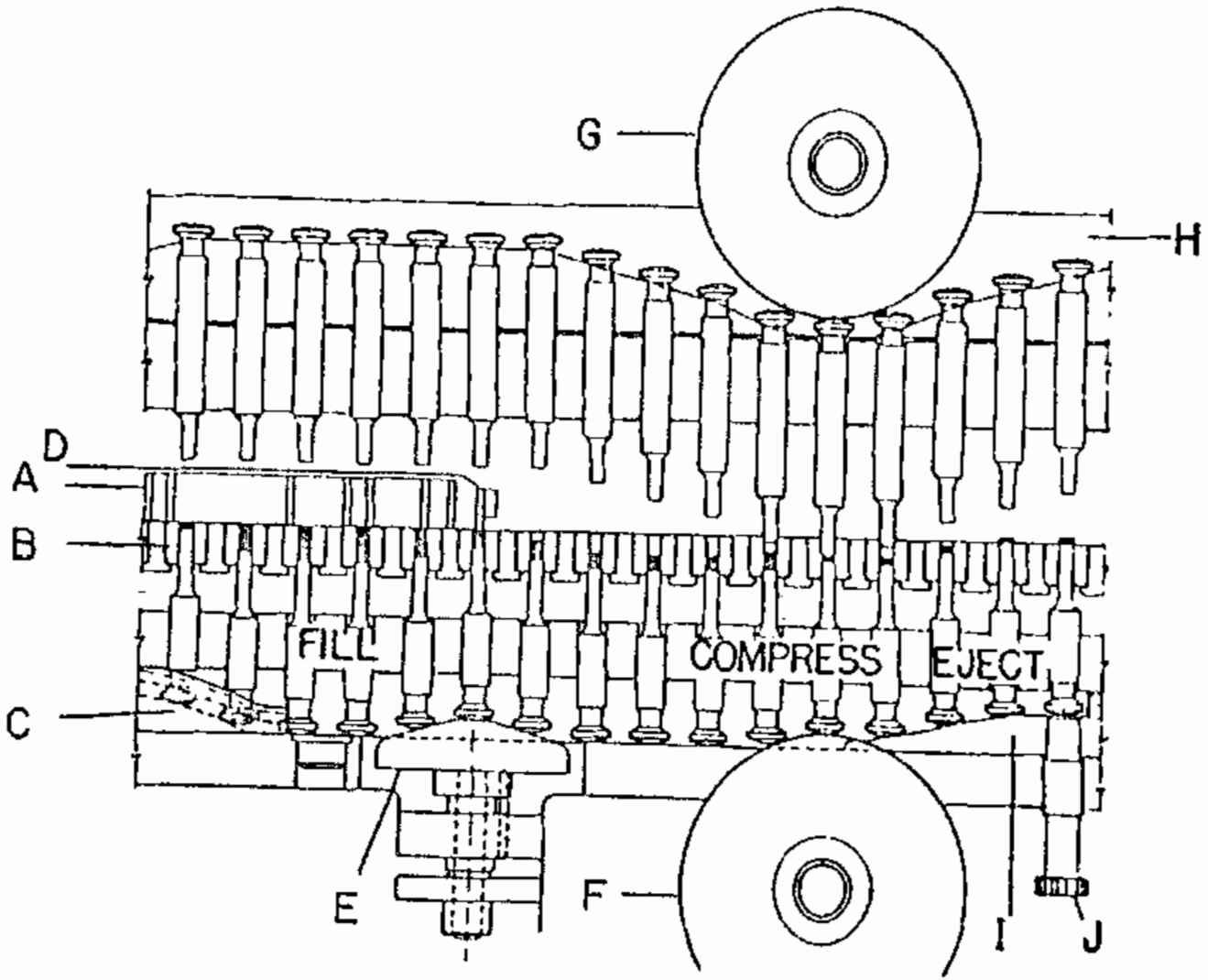

Figure 7. Compression Cycle of Rotary Press (Ref. 1)

One line tender and three packers operate equipment and perform various quality control functions in the room where pack filling occurs. The line tender's duties include 1) making adjustments on process control equipment, 2) helping the packers in troubleshooting line problems, and 3) making sure that the hoppers are filled. Two packers are always at the second belt conveyor inspecting the individual packs. The ones which are defective (missing or broken tablets) are removed from the conveyor and discarded into a cardboard box. The third packer stands in front of the tablet feed chutes and inspects the columns of tablets for defective ones. These are removed by vacuum applied through a small probe attached to a flexible hose. The three line packers switch duties periodically during the shift.

The pack-filling operation is followed by other packaging operations such as additional quality control, addition of literature to the pack, and packing the small packs into larger boxes for shipping.

POTENTIAL HEALTH EFFECTS AND SOURCES OF EXPOSURE

Health hazard controls have been implemented at this facility for control of inhalation exposure to substances which are biologically active in low concentrations. Researchers at OPC have determined that there is very little likelihood that these materials could be absorbed through intact skin. A summary of toxicological data on these substances may be found in Reference 2 under accession number RC8925000 for EE, RC8960000 for MES, and RC8975000 for NOR. No Federal standards for exposure are in effect at this time. However, many of the companies which handle these materials have internal guidelines as to acceptable levels of exposure.

In the following paragraphs, the potential sources of exposure in each step of the manufacturing operations will be qualitatively described. The description will use the terminology and approach followed by Hemeon[3] in analyzing the mechanisms by which contaminants are generated and dispersed in the workplace. The potential sources of exposure are those which in the absence of controls (engineering, proper work practices, and PPE) may result in potentially harmful exposures.

The process of weighing the active ingredients involves scooping the pure material from their shipping packages into smaller containers lined with plastic bags. The pulvation action (or dust generating mechanism) here involves fine dust particles (of the order of 40 microns or less) entrained into the volume of air (airflow) released by the sudden compaction of the powder which was released from the scoop. The amount of dust generated depends upon the total mass of powder in the scoop, the distance of fall, and level of powder in the container which is being filled. Also, the insertion of the scoop into the container full of actives would also result in dust generation by the same mechanism (sudden compaction of the powder). However, the strength of this source is not as large as that from releasing the actives from the scoop.

When actives and excipients are mixed in the processing area, a number of sources may be visualized. The addition of mestranol or ethynylestradiol to

the mixing tank could cause small amounts of these actives to be suspended in the air above the solvent as a result of the shearing action induced by the motion of the particles relative to the air. The same can be said of the dumping of norethindrone into the top of the V-Blender.

After wet mixing and drying have been completed, the active batch is dumped into the capsule. The falling mass of particles would induce an airflow in the general direction of solids flow. This air which contains fine particles "bounces" off the bottom of the receiving vessel and moves in the upward direction. An additional amount of dust would be entrained in the air displaced by powder in the receiving container. Some of this dust created by the dumping process does escape where the capsule mates to the V-Blender.

In the tableting operation, the most significant source of exposure would be the compression of tablets at the two pressure points. The change in bulk density results in a certain amount of air to be driven out which would also entrain some fine powder. The force-flow feed system also generates minor dust emissions resulting from the relatively small amount of compaction that takes place as the powder is beaten about by the rotors and shearing action of the rotary head; the press is designed to control/capture this dust. Finally, if tablets were not dedusted, dust may be suspended as the tablets fall into the receiving container. The mechanism for the generation of dust in this case would be the dispersion of fine powder into the airstream generated by the tablets (in free fall) and fine particles which escape that airstream near its periphery and become suspended in ambient air. This airstream would be deflected when intercepted by the bottom of the receiving container or the mass of tablets already there.

Much less dust is generated in packaging relative to processing and tableting. The potential sources of exposure there include the filling of hoppers with tablets and conveying of the tablets from the hoppers to the feed chutes.

CHARACTERIZATION OF CONTROLS

The objectives of the in-depth survey were to characterize and document the health hazard controls that have been implemented at OPC's steroid (OC tablet) manufacturing operations. The characterization included:

- Observations of the manufacturing operations to qualitatively determine the potential sources of exposure to steroids.
- Assessment of the role of engineering controls in reducing exposures.
- Observation of work practices and obtaining descriptions of worker training programs.
- Conducting air monitoring to determine steroid levels outside personal protective equipment. These levels represent hypothetical exposures which would occur when only the engineered safeguards and work practices are operating.
- Observation of the types of personal protective equipment in use.

Ventilation is an important engineering control at this site. Air velocity (and airflow) measurements were conducted to determine the capture velocity fields of the local exhaust systems at various potential sources. A Kurz Model 441 anemometer was used for this purpose. Measurements of total air supplied and exhausted in each area of interest were not made because OPC-supplied data were deemed adequate.

Air monitoring of steroid concentration levels in each manufacturing area consisted of area samples at previously agreed upon locations and was mainly performed to determine the level of agreement between NIOSH and OPC sampling and analytical procedures. Data on concentration levels in the breathing zone outside respiratory protective equipment were supplied by OPC. The methods used by NIOSH for analysis of the materials of interest are detailed in Appendix A. Briefly, air is drawn at a rate of 3.00 lpm through a 37 mm

Teflon filter millipore FALP 37000 mounted in a cassette. The filters were desorbed with acetonitrile and the extract analyzed by high performance liquid chromatography (HPLC). The limit of quantitation (LOQ) for this procedure is 50 nanograms per filter. Side-by-side area samples were obtained by company and NIOSH investigators, and these samples were analyzed independently. OPC employs a similar air sampling procedure. However, the filters are analyzed by radioimmunoassay (RIA) as described in Appendix A. The LOQ for the RIA technique is 100 picograms per filter.

Work practices were observed while the workers performed their job duties and operated process equipment, and while they donned or removed protective clothing and respiratory protective equipment.

HAZARD CONTROL TECHNOLOGY

GENERAL CONSIDERATIONS

The hazard control techniques of interest are: 1) engineering controls including isolation, ventilation, and automation; 2) work practices which result in lower exposures; 3) monitoring of worker exposures and their health to detect and correct problems as they occur; and 4) personal protective equipment that is effective in further reducing exposures to levels that are considered acceptable by the company.

ENGINEERING CONTROLS

Preweighing of Ingredients

The excipients are preweighed into fiber drums lined with plastic bags at a location remote from the steroid facility. They are brought to the material staging area immediately before a batch is to be mixed. The operation of preweighing of excipients was not observed. However, it may be presumed that the health hazards associated with preweighing of excipient are minor and that the controls are not as stringent as those employed when handling steroids.

Active ingredients are preweighed in the preweigh room within the confines of a Type A hood manufactured by the Baker Company. Figure 8 is a front view of the hood.

Air velocities at the hood face averaged approximately 50 fpm (using the rotating vane anemometer) so that a total of approximately 620 cfm of air is moved through this hood. The design airflow through this hood is 575 cfm. The exhausted air is ducted to the dust collector, an American Air Filter, FABR, pulse unit, which has a rated particulate filtration efficiency of 99.9 percent at 1 um. The capture characteristics of the hood are such that an air velocity of 100 fpm is obtained at the front end of the balance. This is judged adequate to capture fine dust that may be generated by transferring ingredients from one container to another. Of course, when the worker stands

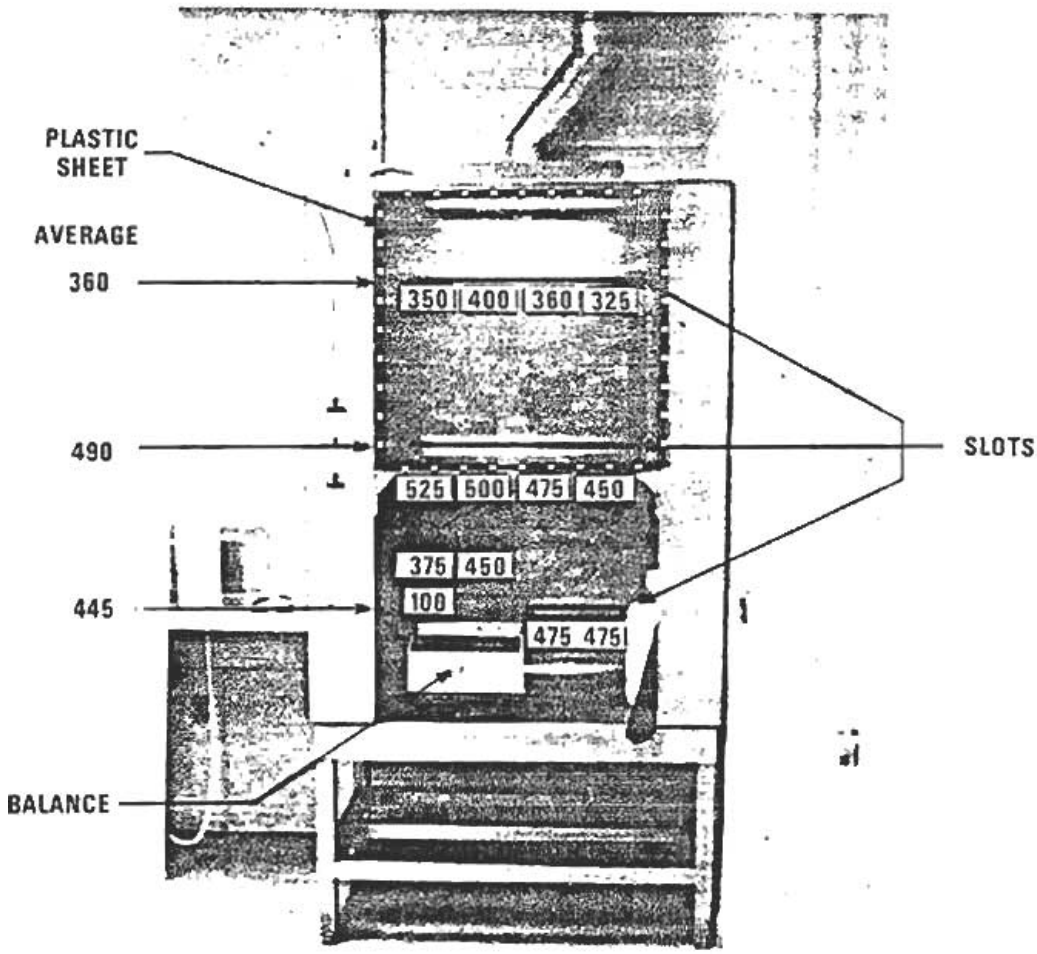

Figure 8. Front View of Preweigh Hood

Note: Numbers Indicate Local Velocities in fpm

in front of the hood, the air velocity field to his immediate left and right are altered. However, the streamlines would be expected to reform and produce about the same capture velocities at the critical points.

A plan view of the preweigh room is given in Figure 9. Air is supplied to the room at a rate of 9.0 room volumes per hour (RVPH) and exhausted (through the hood) at the rate of 11.3 RVPH. Thus, a negative pressure related to its surroundings exists in this room.

If any of the two access doors is open, a switch attached to the door will cause the motorized dampers, which control air supply, to be closed.

Granulation

Excipients are transferred to the V-Blender from their containers in the material staging room using the VAC-U-MAX system shown in Figure 2, thus isolating the technician from the processor room. When compared to direct dumping of the materials, use of this transfer system drastically reduces the dust generation rate. A canopy hood is used to capture dust at the location where the wand is used to empty the drums of excipients. This canopy hood also constitutes the only point where the air is exhausted from the room at the rate of 9 RVPH. The air supply is distributed from two ceiling diffusers at the rate of 7.5 RVPH. Thus, a negative pressure relative to its surroundings exists in this room.

Norethindrone is added to the blender directly. Mestranol or ethynylestradiol are dissolved in the granulating liquid which is premeasured and placed in the mixing tank before active ingredients are added. General dilution ventilation is provided in this room as shown in Figure 10. The supply and exhaust grilles (except for air exhausted to the dust collector) are at ceiling level. While at first glance it may be thought that locating the exhaust grille at ceiling level may cause bypass, company officials emphasized that the supply grilles are designed to deliver the air supply to within a few feet of floor level. Air at the rate of 1.6 RVPH is exhausted to the dust collector and 4.1 RVPH is exhausted to the air handling system through the

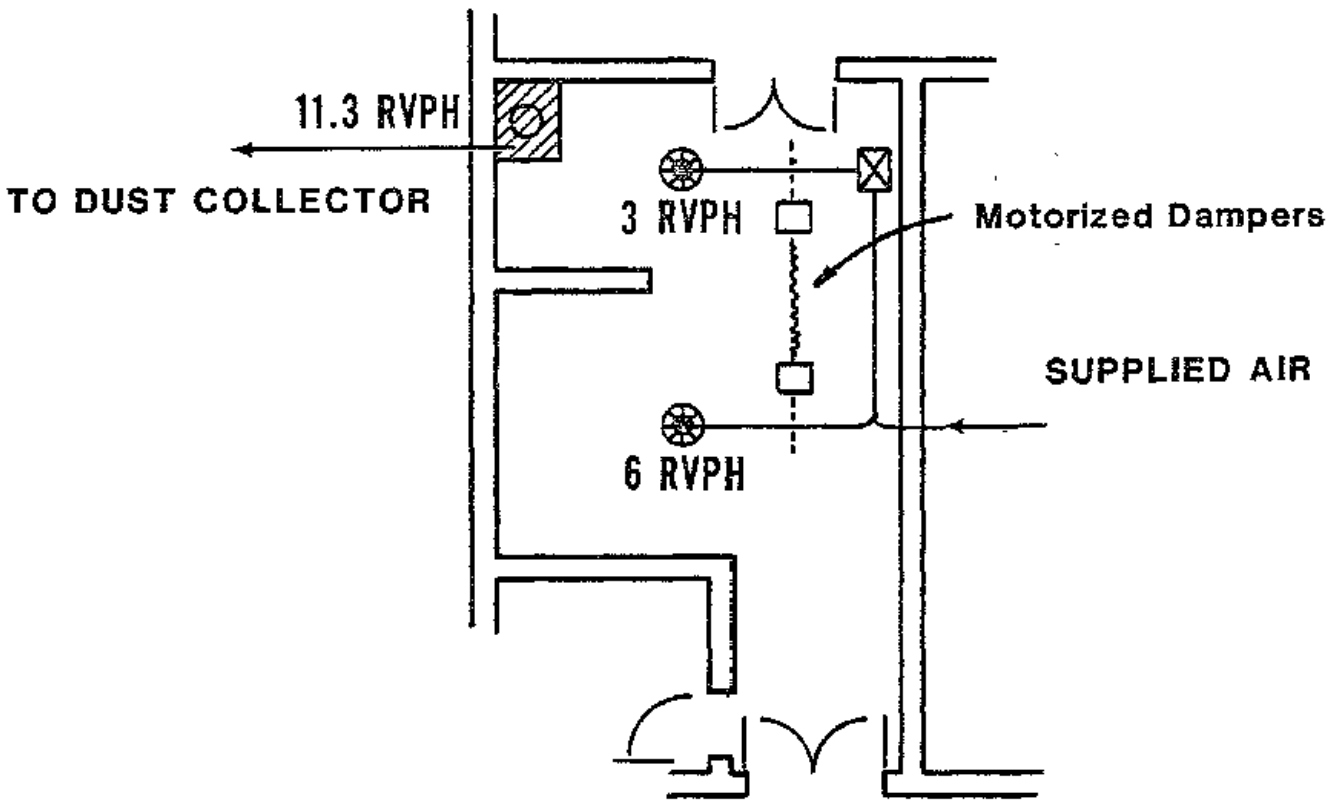

Figure 9. Plan View of Preweigh Room and General Ventilation Scheme

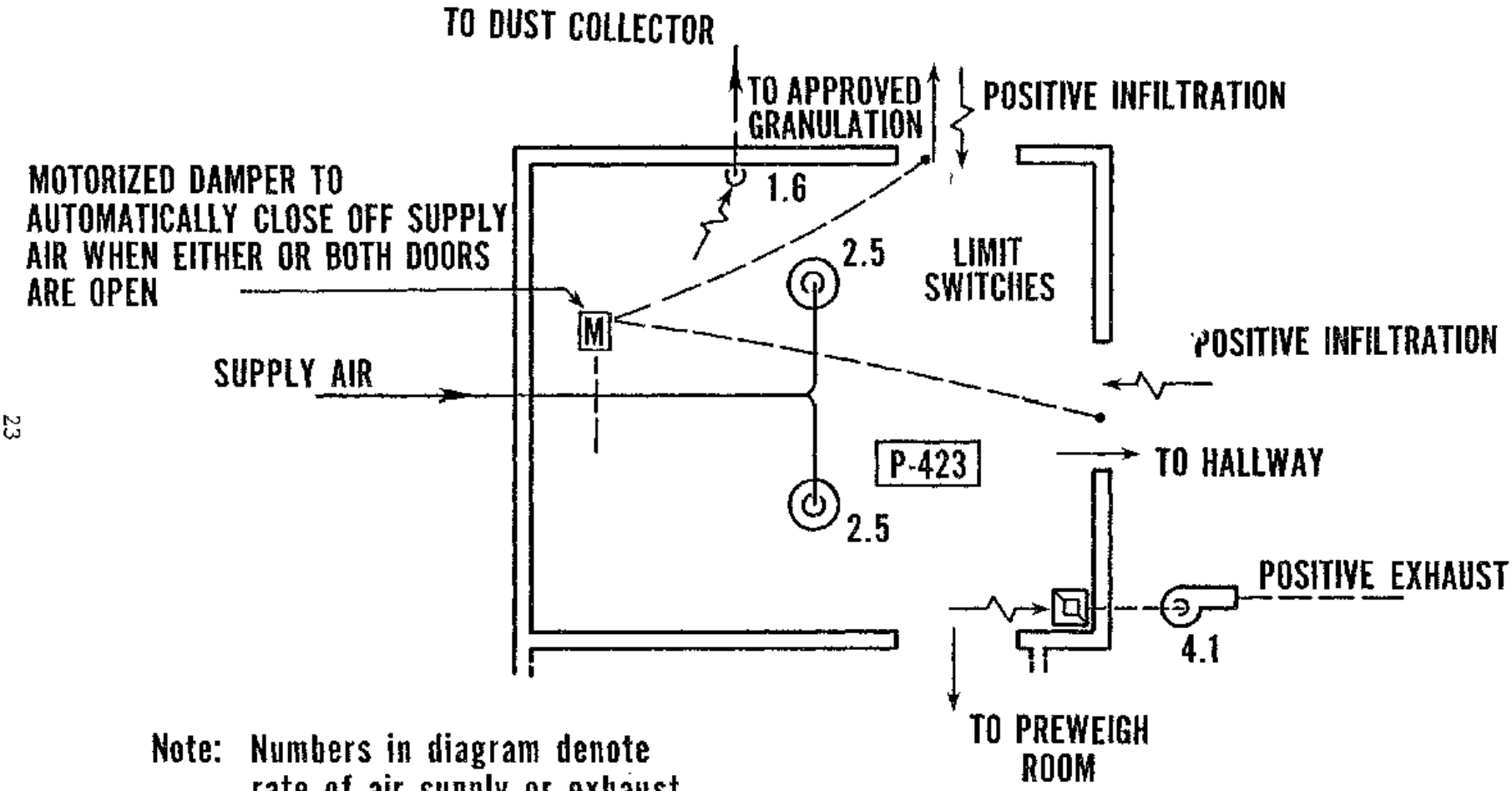

Figure 10. Plan View of Processor Room With Ventilation Controls

Note: Numbers in Diagram Denote Rate of Air Supply or Exhaust in RVPH

grille in the ceiling. Air is supplied at the rate of 5 RVPH through the two supply grilles in the ceiling. The motorized damper shuts off the air supply when either the double door leading to the hallway or the one leading to the room where approved granulation is stored or both are opened. Switches, located at these doors, activate the motorized damper. Shutting off the air supply when the doors are opened has the effect of preserving the principle of positive air infiltration into the room where the processor is located.

The air exhausted to the dust collector is used as a vacuum source for the mobile local exhaust semicircular slot hood used to control dust when dumping the dry granulation from the blender to the capsule. A picture of the mobile slot hood appears in Figure 11. Measurements of the capture velocities of this hood were not possible. However, when using this configuration to achieve dust control, the desired control velocities (between 75 and 100 fpm) at any given distance, for example at a distance of 6 inches from the hood face, may be obtained by adjusting the total airflow exhausted.

The process of granulation as carried out at OPC may in itself be considered an engineering control since the number of transfer points (or processing steps which have a potential for dust generation) have been reduced from about 7 or 8 for less advanced processing systems, to only 2. The two points are the addition of active ingredients and the dumping of dry granulation.

There are additional safety devices in the blender area. Access to the immediate vicinity of the blender is restricted by two gates (one in front and one in back of the blender) to prevent the possibility of workers being struck by the rotating blender. The gates are equipped with electrical switches which prevent them from being opened unless power to the blender is off.

All electrical equipment in the blender area is of the explosionproof-type and designed for use in hazardous locations where explosions or fires may occur as a result of 1) the buildup of air concentrations of the granulating liquid in case of failure of the ventilation system or 2) the ignition of the air/vapor mixtures by sparks generated in electrical equipment in the event of spillage of the granulating liquid.

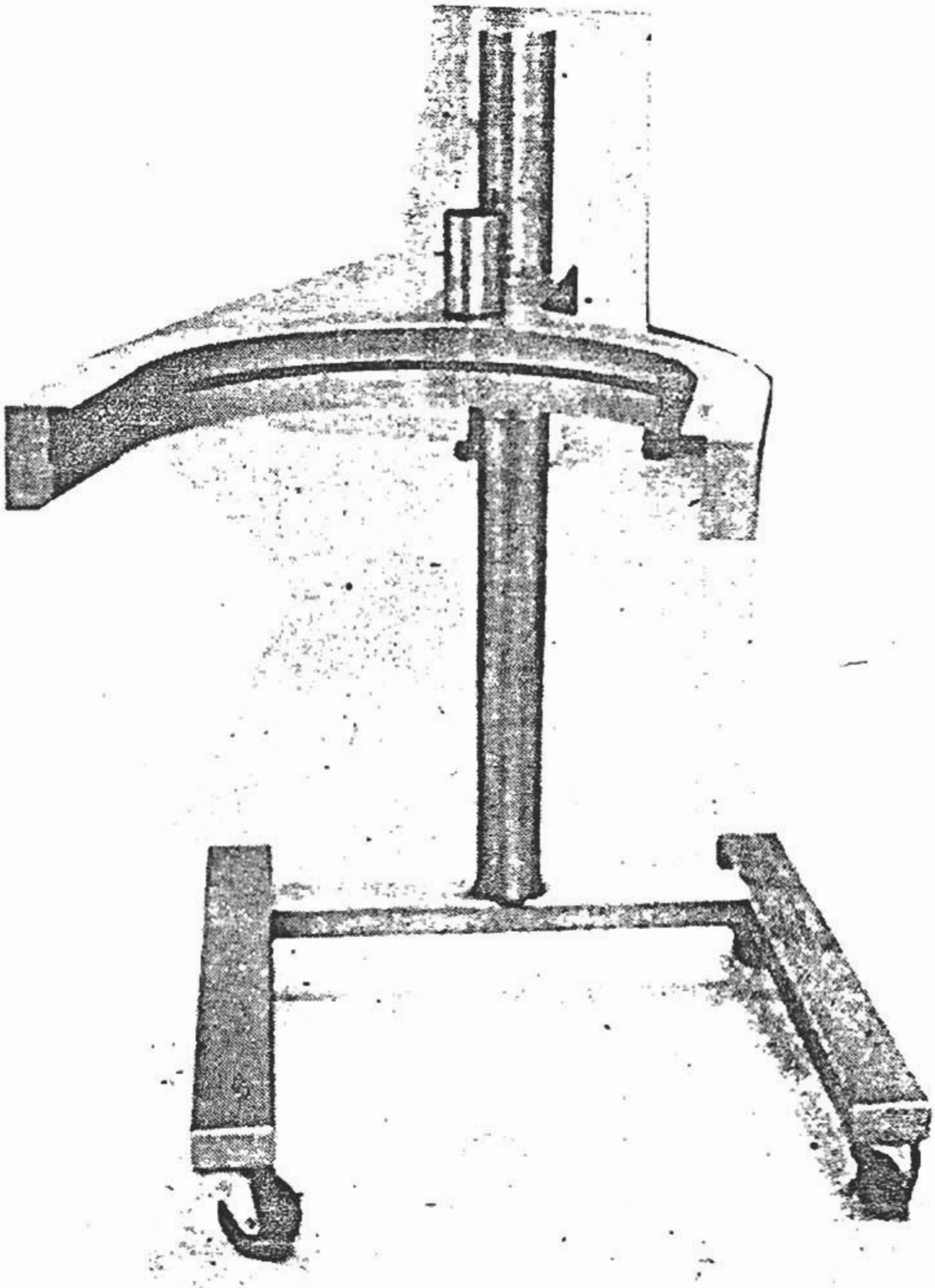

Figure 11. Flanged Slot Hood to Control Dust Generated in Dumping Granulation from Blender to Capsule

Tableting

The engineering controls in this area consist of 1) a granulation delivery system that is totally enclosed and 2) general and local ventilation.

A capsule containing granulation is wheeled into the tableting room on a dolly from the approved product storage area. It is raised, inverted, and positioned over a closed chute leading to the feed hoppers of the press by means of an electric hoist mounted on a monorail suspended from the ceiling. The capsule is bolted to the chute with a gasketed flange which prevents product leakage at this point. Flow from the capsule to the press is controlled by a butterfly valve in the capsule and closed screw conveyors which deliver the granulation to the two feed hoppers at the top of the press. The delivery system is shown schematically in Figure 4. The rotary head of the Manesty press is enclosed by four double glazed glass panels, one on each side as shown in Figure 4.

The tableting machine and peripheral equipment are ventilated by several hundred cfm. The two pressure points, where the potential for dust generation is at a maximum, are ventilated by one "slot" hood which is about 2 by 0.5 inches. An average velocity of about 500 fpm was measured at one of these slots. The rotary head enclosure is ventilated at two points as shown in Figure 4. The airflow in these two pipes is estimated at between 75 and 150 cfm. Finally, air is exhausted from a plenum directly below each of the two vibratory conveyors/dedusters on the left and right sides of the machine. As a result of this exhausted air, "control" velocities on the order of 300 feet per minute are achieved at point (A) where the tablets exit the rotary head enclosure, 100 fpm directly above the partially open area (B) where the tablets enter the conveyor, and about 100 fpm at the open area (C) where the tablets exit the conveyor. All these points are marked on Figure 4.

The general ventilation scheme in the tableting room is shown in Figure 12. Air is supplied at the rate of 20.7 RVPH of which 15.8 RVPH are distributed through grilles in the ceiling and about 5 RVPH are used to ventilate the area immediately above the tableting machine in conjunction with 6.75 RVPH that is

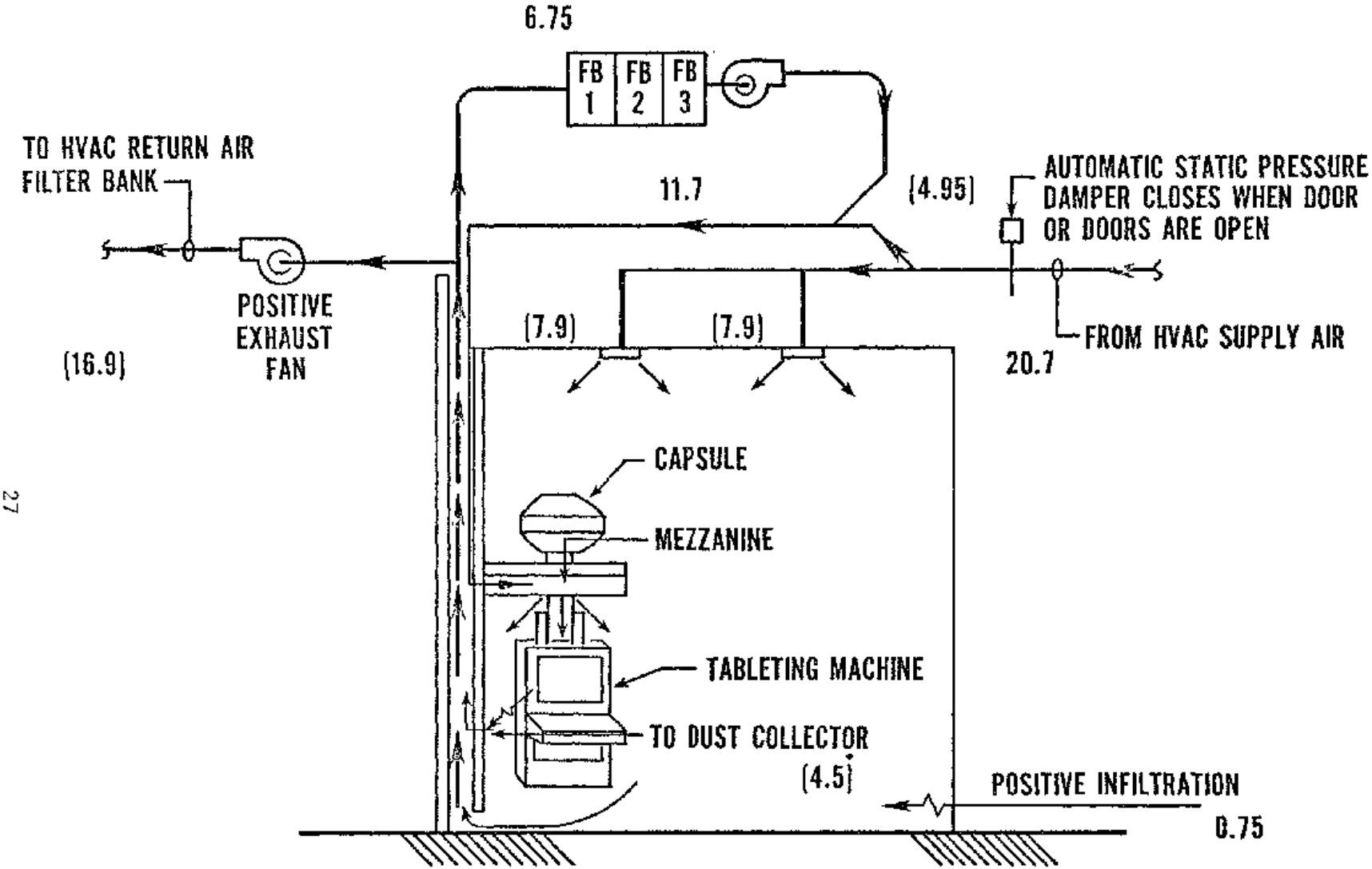

Figure 12. Schematic Cross Section of Tableting Room

recycled after removal of dust. About 17 RVPH are exhausted to the air handling system through a slot at floor level while 4.5 RVPH are exhausted to the dust collector from the local exhaust devices that are associated with the tableting machine and previously discussed. A portion of the exhausted air is recycled and dust is removed by 3 filter banks in series. The first two consist of "prefilters" while the third is a HEPA filter.

Under normal conditions, the doors to the room are closed. An air balance around the room indicates that more air (about 0.75 RVPH) is exhausted than supplied in order to maintain a positive infiltration into the room. If a door to the room in opened, switches attached to the door would cause the motorized supply air damper to close so that positive infiltration of air from the corridor is maintained.

Packaging

There are a number of local exhaust ventilation controls incorporated into the circular pack filling machine. The three hoppers containing OC and placebo tablets are covered and are exhausted at an estimated rate of 15 cfm each by "elephant trunk" hoses that are attached to the covers. The three vibratory conveyors which transfer tablets from the hoppers to the device which feeds the chutes with tablets are ventilated at an estimated rate of 25 cfm each. The conveyors are covered with rectangular hoods through which the air is exhausted at an estimated rate of 25 cfm.

Air is exhausted from the enclosed space between the end of the conveyors and the device which feeds the chutes at an estimated rate of 100 cfm. Air velocities in the range of 100 to 150 fpm were measured in the annular spaces between stationary and moving parts. The space in front and in back of the tubes connecting the chutes to the "blocks" which positively feed the individual circular packs is ventilated by two small circular hoods at an estimated rate of 120 cfm through each. Control (air) velocities between 50 and 80 fpm were measured in an imaginary vertical plane which intersects the horizontal plane of the conveyor. Capture velocities between 30 and 40 fpm

were measured at the fringes where contaminants are not very likely to be dispersed.

Clean air is supplied to the filling room from four grilles in the ceiling at a rate of 12.0 RVPH. Air is exhausted from the room to the air handling system at a rate of 10.2 RVPH from two exhaust grilles. An additional 4.1 RVPH is exhausted to the dust collector from 3 locations. One of these is the manifold which provides local exhaust ventilation at various points in the pack filling operation. The balance of the air (2.3 RVPH) enters the room through positive infiltration from the adjacent room where packaging is completed. Similar rates of air supply and exhaust are also used in that area.

Air Handling Systems

Air supplied to and exhausted from the manufacturing rooms, corridors, and packaging rooms is handled by one of two central air handling units. Each air handling unit is similar in design with respect to filters and airflows. These air handling units working in conjunction with localized exhaust fans, secondary recirculation air units, and a centralized dust collector provide the required building ventilation.

All sources which are likely to produce relatively "concentrated" streams are exhausted to the dust collector. These sources include the hood in the preweigh room, the portable hood used when dumping granulation from the blender, local exhaust systems associated with the tableting machine, and those associated with the circular pack filling machine. The dust collector is a device with a particle filtration efficiency of 99.9 percent with respect to dust particles of 1.0 micron in diameter.

Air exiting the dust collector is combined with building return air before treatment and conditioning. The air passes through two prefilters and one HEPA filter with a removal efficiency of 99.97 percent with respect to particles at 0.3 microns in diameter. A minimum of approximately 10 percent of this building air is exhausted to the outside. Fresh outside air in a quantity slightly higher than was exhausted is then mixed with the remainder

(approximately 90 percent). This air is prefiltered, cooled, and HEPA filtered. It constitutes air returned to the various areas served by the system. Reheat coils and humidifiers are installed in the ductwork which serves various rooms.

Access to Processing Areas

Access to all processing areas (granulation processing, tableting, and preweighing) is through the locker rooms. The men's locker is diagramed in Figure 13. The worker removes his street clothes in the locker room and dons personal protective equipment which is picked up from the "wet suit" room. The worker then enters processing from the entry door shown in the diagram. The worker returns through another door leading to the suit wash, where jets of water remove particulate from the outside surfaces of the suit. The worker proceeds through the air blast to the "wet suit" room where he takes the vinyl suit off and hangs it to dry in an appropriate location. The design ventilation airflows and air distribution scheme are shown in Figure 13.

WORK PRACTICES

New employees receive on-the-job training and indoctrination in good manufacturing practices (GMP's) and safety. Manuals have been written and these are available for use by both new and old employees.

On-the-job training consists of a gradual introduction of the new worker to the job together with a gradual building of his/her competence. The first time that a worker is assigned to a given operation, he/she observes it being performed by a senior technician. The second time involves active participation with the senior technician. The third time he/she performs the work while being observed or monitored by the senior technician. Usually, the new worker is able to perform the job duties adequately on the fourth time.

In the area where estrogens are handled, work activities are classified with respect to risk of exposure. High risk activities are those which involve significant potential employee exposure. Included in these activities are

	AIR SUPPLIED CFM	AIR EXHAUSTED CFM
Suit Wash	55	55
Air Blast	50	50
Wet Suit	100	250
Shower	100	100
Toilet	150	150
* Locker Room	750	500

* 250 cfm are transfer air to toilet and shower

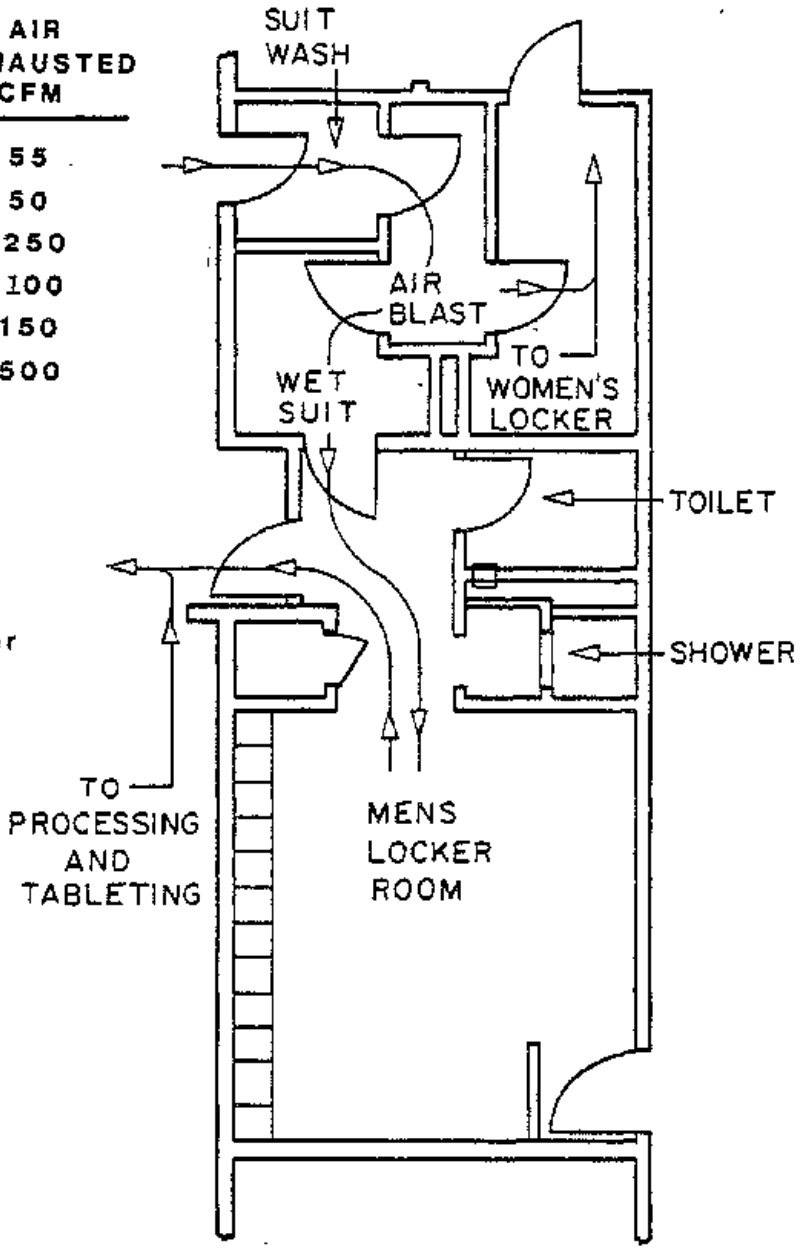

Figure 13. Controlled Access to High Risk Areas

sampling and analysis of pure active ingredients, preweighing, processing, tableting, and cleanup operations in both processing and tableting. Moderate risk activities are those which involve moderate potential employee exposure. These include maintenance activities, filter changing, tablet and granulation analysis, and direct supervision of activities with high or moderate risk. Low risk activities are those which involve a minimal potential for employee exposure. These include tablet inspection, handling of closed containers, circular pack filling and reclaiming, and filling line cleanup.

A safety procedure has been written which specifies personal protective equipment and administrative controls required for each category of risk. A rotation policy in high risk activities has been implemented which specifies that for every 10 hours of high risk work, the workers must stay out of the area and perform entirely different activities for 48 hours. Fertile females are excluded from high risk activities because steroids are considered to be known teratogens.

In addition to the safety procedure mentioned above, all "batch" sheets include detailed requirements for personal protective equipment. "Refresher" sessions are held regularly which include the showing of movies on the use, maintenance, and storage of respirators. Also, information on new equipment is presented at these sessions.

Workers in the estrogen area are educated in the health effects of exposure to estrogens by a company physician and the company safety specialists. They also explain the importance of complying with safety requirements. Work practices are regularly audited by supervisors. Discussions of training requirements and manufacturing operations are held once a month.

MONITORING

Company Activities

Environmental and medical monitoring of employees is an ongoing activity at OPC. Environmental monitoring consists of periodically obtaining area and

personal samples in various areas namely, processing, tableting, and packaging. The samples are collected on 0.5 micron Teflon filters and analyzed by radioimmunoassay (RIA). A short description of this technique is given in Appendix B. The limit of detection of RIA is 100 picograms per filter. The samples are obtained at an airflow rate of 4.0 lpm for 6 to 8 hours depending on the duration of the activity. All samples are analyzed for MES, NOR, and EE. Even though only one estrogen (MES and EE) may be present in one sample, the analysis for the other is a quality control procedure.

A plan view of the Ortho-Novum facility appears in Figure 1. The locations of the general area samples are shown in the Figure 14. At most of these locations, the sample is obtained at a distance of approximately four feet above ground level and the pump is hung against the wall. Typical area results obtained for the general area and personal samples are shown in Tables 2 and 3, respectively. All concentrations represent 8-hour time-weighted averages (TWA). Therefore, if the duration is lower than 8 hours, the TWA concentration would be lower than that actually measured.

Table 2. Typical Area Sample Results as Previously Determined by OPC

Area/Room	Location No.	Avg. MES Conc., microgram per cu.m.	No. of Samples, MES	Avg. NOR Conc., microgram per cu.m.	No. of Samples, NOR
Preweighing	33	0.013	3	0.14	3
Processing	35	1.18	2	1.60	4
	36	0.053	2	1.40	4
	37	0.054	2	2.20	4
Tableting	40	0.15	4	2.85	4
	41	0.10	5	1.74	5
	42	0.01	3	0.37	3
Packaging	15	0.003	1	0.02	1
	16	0.008	4	0.27	4
	17	0.005	5	0.26	5
	18	0.01	6	0.41	6

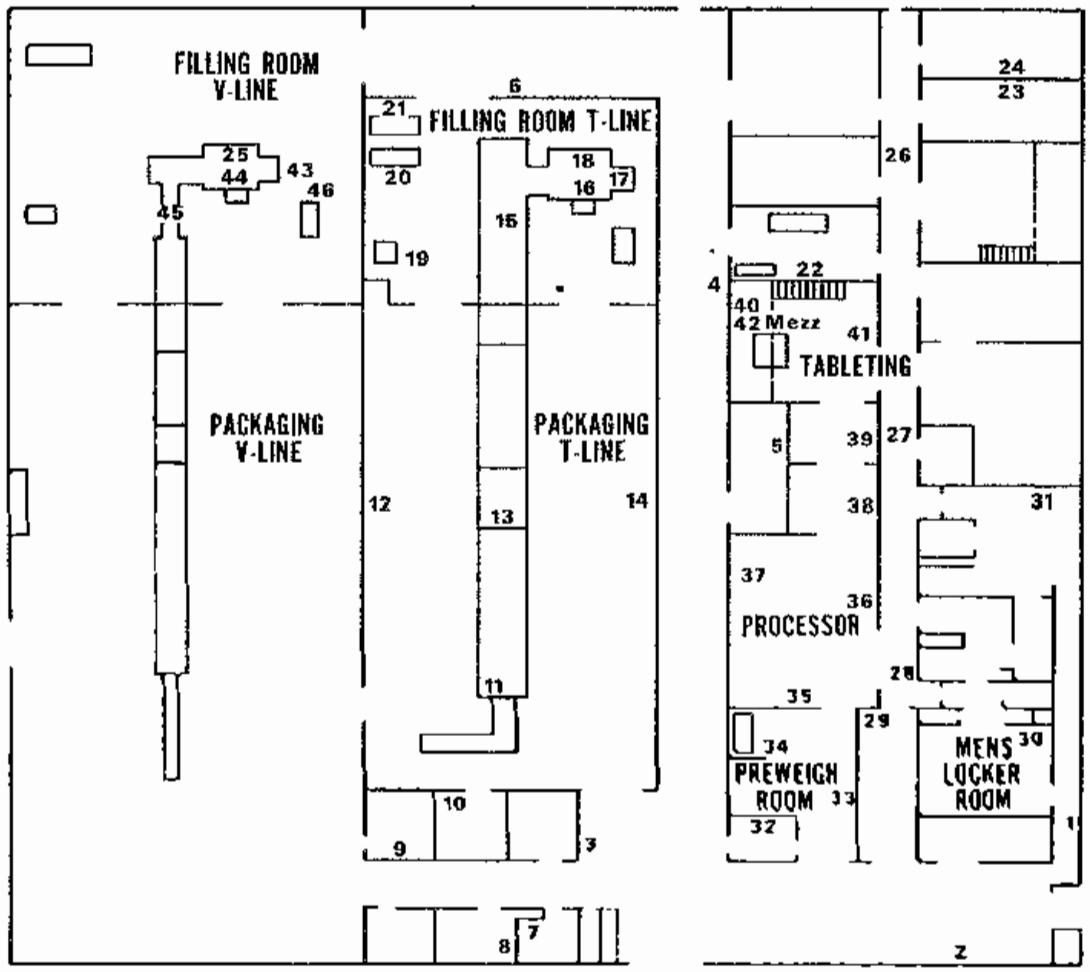

Figure 14. Plan View With Sampling Locations

Note: Numbers Indicate Area Sample Locations

Table 3. Typical Breathing Zone Levels for Personal Samples as Previously Determined by OPC

Area/Room	Where Taken	MES Conc., microgram per cu.m.	No. of Samples, MES	NOR Conc., microgram per cu.m.	No. of Samples, NOR
Tableting	Inside Vinyl Suit	0.02	4	0.32	4
	Outside	1.71	2	31.80	2
Packaging*		0.02	1	0.48	1

* Actual breathing zone levels would be slightly higher than one-third the values given since three workers rotate this position.

Medical monitoring of employees is conducted routinely. Physical examinations are administered only to workers who may exhibit symptoms of overexposures to steroids. Every 6 months, each worker fills out a questionnaire to determine whether overexposures may have occurred.

Monitoring During NIOSH Survey

Side-by-side area samples were obtained by both NIOSH and OPC during the survey. Personal samples were obtained by OPC for workers in processing and tableting. All OPC samples were analyzed by RIA. The personal samples were taken at the breathing zone of workers outside of the air-supplied suit and as such represented environmental levels of contaminants with only the engineering controls in operation. Of course, actual worker exposures would be the outside-the-suit levels divided by the protection factor for the PPE.

General area sample results for the three areas of interest, namely, processing, tableting, and packaging are presented in Tables 4, 5, and 6 respectively. The general area samples taken by both NIOSH and OPC served to establish the degree of correlation between the two sampling and analytical methods. Because of differences in limits of detection, only norethindrone

concentrations in the processing and tableting areas could be compared. A statistical comparison of the data at these locations shows that for a log-log plot of the data presented in Table 7, the slope is not significantly different from unity and the intercept is not significantly different from zero. The correlation coefficient is 0.905. It is apparent then that breathing zone samples results by Ortho (reported in Table 8) would be in close agreement to such samples taken by NIOSH. It is noteworthy that, in general, sample results in processing are about 10 times higher than those in tableting and that the samples in tableting are about 10 times those in packaging.

Table 4. General Area Sample Results in the Processing Room While Mixing Ortho-Novum(R) 1/35 (NOR/EE)

Date	Location Number	Sampling Rate Liters Per Minute		Duration of Sampling, Minutes		Concentration, micrograms per cu.m.					
						MES		EE		NOR	
		NIOSH	OPC	NIOSH	OPC	NIOSH	OPC	NIOSH	OPC	NIOSH	OPC
6/14	28	3.1	-	557	-	ND	-	ND	-	0.27	-
	35	3.7	4.0	566	561	ND	0.0050	ND	0.1092	17.81	5.35
	36	3.7	4.0	569	576	ND	0.0019	ND	0.0127	3.19	0.55
	37	3.7	3.0	562	300	ND	0.0774	ND	0.1930	3.03	13.33
	37	3.7	-	562	-	ND	-	ND	-	3.49	-
6/15	28	3.7	-	519	-	ND	-	ND	-	0.28	-
	35	3.7	4.0	523	532	ND	0.0015	ND	0.3073	12.93	11.13
	36	3.6	3.3	530	531	ND	0.0355	ND	0.2768	12.50	17.23
	37	3.5	4.0	522	532	ND	0.0296	ND	0.2429	15.45	11.41
	37	3.6	-	522	-	ND	-	ND	-	9.89	-

Table 5. General Area Sample Results While Tableting Modicon (NOR/EE)

Date	Location Number	Sampling Rate Liters Per Minute		Duration of Sampling, Minutes		Concentration, micrograms per cu.m.					
						MES		EE		NOR	
		NIOSH	OPC	NIOSH	OPC	NIOSH	OPC	NIOSH	OPC	NIOSH	OPC
6/16	27	3.7	-	465	-	ND	-	ND	-	ND	-
	40	3.7	3.3	475	473	ND	0.0010	ND	0.0030	0.31	0.1858
	40	3.7	-	474	-	ND	-	ND	-	0.15	-
	41	3.7	4.0	468	465	ND	0.0030	ND	0.0123	0.44	0.4301
	42	2.9	4.0	472	468	ND	0.0019	ND	0.0081	0.52	0.3632
	47	3.7	4.0	480	522	ND	0.0026	ND	0.0114	0.44	0.4215
6/17	27	3.7	-	473	-	ND	-	ND	-	ND	-
	40	3.7	2.7	462	471	ND	0.0024	ND	0.0082	0.44	0.2987
	40	3.7	-	462	-	ND	-	ND	-	0.45	-
	41	3.7	4.0	471	466	ND	0.0029	ND	0.0122	0.48	0.2843
	42	3.7	4.0	459	470	ND	0.0019	ND	0.0056	0.47	0.2660
	47	3.7	4.0	472	468	ND	0.0061	ND	0.0304	0.42	0.7051

Table 6. General Area Sample Results While Packaging

Date	Location Number	Sampling Rate Liters Per Minute		Duration of Sampling, Minutes		Concentration, micrograms per cu.m.					
						MES		EE		NOR	
		NIOSH	OPC	NIOSH	OPC	NIOSH	OPC	NIOSH	OPC	NIOSH	OPC
	OPERATION: Packaging (V-Line); PRODUCT/INGREDIENTS: 1/35 (NOR/EE)										
6/14	25	3.7	4.0	448	440	ND	0.0004	ND	0.0083	ND	0.3100
	44	3.7	3.3	440	437	ND	0.0005	ND	0.0026	ND	0.0901
	45	3.69	-	435	-	ND	-	ND	-	ND	-
6/15	25	3.7	4.0	281	280	ND	0.0006	ND	0.0021	ND	0.0357
	44	3.7	4.0	283	282	ND	0.0014	ND	0.0012	ND	0.0266
	45	3.9	-	288	-	ND	-	ND	-	ND	-
	OPERATION: Packaging (T-Line); PRODUCT/INGREDIENTS: 1/50 (NOR/MES)										
6/16	15	3.7	-	459	-	ND	-	ND	-	ND	-
	16	3.7	4.0	457	187	ND	0.0015	ND	0.0007	ND	0.0401
	18	3.6	4.0	459	472	ND	0.0013		0.0004	ND	0.0370
6/17	15	-	-	-	-	-	-	-	-	-	-
	16	3.7	4.0	470	482	ND	0.0045	ND	0.0006	ND	0.1712
	18	-	-	-	-	-	-	-	-	-	-

Table 7. Data Used to Compare Sampling and Analytical Results

Date	Location No.	NOR Concentration Micrograms per cu.m. NIOSH	Ortho
6/14	35	17.81	5.35
	36	3.19	0.55
	37	3.26*	13.33
6/15	35	12.93	11.13
	36	12.50	17.23
	37	12.67*	11.41
6/16	40	0.23*	0.186
	41	0.44	0.430
	42	0.52	0.363
	47	0.44	0.421
6/17	40	0.44*	0.300
	41	0.48	0.284
	42	0.47	0.266
	47	0.42	0.705

* Average of a pair of samples taken at the location.

Table 8. Breathing Zone Levels Outside PPE

Date	Operation	Product/ Ingredients	Sampling Rate Liters Per Minute	Duration of Sampling, Minutes	Concentration, micrograms per cu.m. MES	EE	NOR
6/14	Processing	1/35 (NOR/EE)	3.3	409	0.0043	0.1971	12.89
6/15	Processing	1/35 (NOR/EE)	3.3	281	0.0560	0.5974	20.83
6/16	Tableting	Modicon (NOR/EE)	3.3	319	0.0031	0.0230	0.98
6/17	Tableting	Modicon (NOR/EE)	3.3	259	0.0604	0.2200	3.76

The small number of personal samples taken in each area does not allow an accurate computation of the mean breathing zone level for each job category and obtaining an accurate estimate of the confidence limits pertaining thereto. However, the data are useful in qualitatively estimating the order of magnitude of exposures in each location. With these limitations in mind, workers in processing had a geometric mean breathing zone level of 16.4 micrograms per cu.m. with respect to NOR, while those in tableting had a geometric mean level of 1.92 micrograms per cu.m. during the NIOSH survey. Actual exposures would be 1/100 to 1/1000 those levels as explained later.

All blank samples and samples taken by NIOSH in the locker room showed nondetectable levels of the contaminants. Those obtained by OPC in the locker room showed levels between 0.06 and 0.08 micrograms per cu.m. The levels of mestranol and ethinylestradiol were between 1/30th and 1/1000th those values.

PERSONAL PROTECTIVE EQUIPMENT

Workers performing high risk activities don air-supplied vinyl suits and disposable rubber gloves. The vinyl suits have overshoes attached. The worker exits the high risk area through the suit wash where jets of water wash the dust off the suit before it is taken off.

For moderate risk activities, the worker dons a disposable suit, rubber gloves, and shoe covers. A respirator which is approved for dusts, fumes, and mists having a TLV less than 0.05 mg per cu.m. is also worn.

Workers in low risk activities wear disposable rubber gloves and disposable dust respirators approved for protection against fibrosis and pneumoconiosis.

Air-supplied suits have an estimated protection factor of 2000 or more.[4] Achieving the higher levels is dependent upon maintaining the outside as well as the inside surfaces of the suit free from contamination. Also important is maintaining the clean air distribution and delivery hoses and associated connect/disconnect fittings free from contamination. Data reported in Table 3

seem to indicate that the air-supplied vinyl suit has a protection factor of 100.

CONCLUSIONS

The OC tablet manufacturing operations at OPC may be considered state-of-the-art technology. A system of health hazard controls has been implemented to reduce worker exposures in processing, tableting, and packaging. The important engineering controls include general and local exhaust ventilation for all three operations, a reduced number of material transfer operations in processing, and an enclosed powder delivery system in tableting.

Suitable work practices are attained through on-the-job training for new workers in addition to emphasizing the safety aspects of each job. Batch sheets for each product specify personal protection required through each step of the operation. Health hazards are explained to the workers by a company physician and the safety specialists.

Environmental and medical monitoring of employees is performed routinely. Employees are required to fill out medical questionnaires every 6 months. A physical examination is administered to those who exhibit symptoms of overexposure. Data obtained by OPC before the NIOSH survey indicates that outside-the-suit levels of 31.80 micrograms NOR per cu. meter and 1.71 micrograms MES were measured in the tableting room. Filling machine workers breathing zone levels outside respiratory protective equipment were 0.48 micrograms NOR and 0.02 micrograms MES per cubic meter. Data obtained by OPC during the NIOSH survey indicate that processing worker's breathing zone levels outside the vinyl suit were 16.40 micrograms NOR and 0.306 micrograms EE per cubic meter.

REFERENCES

1. Lachman, L., H.A. Lieberman, and J.L. Kanig: The Theory and Practice of Industrial Pharmacy (2nd Edition). Lea and Febiger, Philadelphia (1976).

2. Registry of Toxic Effects of Chemical Substances. R.J. Lewis, Sr., and R.L. Tatken, Editors, Vol. 2, DHHS, PHS, CDC, NIOSH (February 1982).

3. Hemeon, W.C.L.: Plant and Process Ventilation. Industrial Press Inc., New York (1962).

4. Pritchard, J.A.: A Guide to Industrial Respiratory Protection. U.S.DHEW, PHS, CDC, NIOSH, June 1976.

APPENDIX A
ANALYTICAL PROCEDURES

HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

The procedure described below outlines a typical analysis of air samples by high performance liquid chromatography (HPLC). This procedure is concerned with the synthetic steroids mestranol, norethindrone, and ethinylestradiol.

The samples are typically extracted with acetonitrile and agitated on a sonic bath at 60°C for 1 hour. The samples are filtered through FALP filters, concentrated by solvent evaporation, and analyzed by HPLC.

The HPLC conditions are as follows:

Column - Waters Radial Pak A in a radial compression module
Solvents - 40 percent acetonitrile/60 percent water isocratic
Flow rate - 3 mL/min

The eluting peaks are measured by two UV detectors and one fluorescence detector in series. The UV detectors (Waters 450) are set at 190 nm for detection of norethindrone and 254 nm for detection of mestranol. The fluorescence detector is a Schoeffel FS970 set at 210 nm excitation with a 340 nm emission filter.

RADIOIMMUNOASSAY

The filters are extracted with a suitable solvent (e.g., diethyl ether) and an aliquot is placed in assay tubes. Appropriate antiserum solution and a radioactive tracer are added to samples and standards.

After thorough mixing and incubation, bound and free steriods are separated, and the bound steriod is placed in scintillation vials and the radioactivity measured. Suspected contaminants (e.g., progestins) are checked for cross-reactivity since these are usually present on the same filters.