

Buildings in which drugs are manufactured must be of suitable size and construction to house the necessary equipment and materials in such a manner that cross-contamination or mixup is avoided. In the better plants, provisions are made for cleaning the air and controlling temperature and humidity. One example of the great care that is taken to assure the most sanitary conditions possible is the sterilization of areas used for the production of parenteral products. Much of the equipment used in these plants is custom-designed and considerable engineering ingenuity is required.

Of paramount consideration are cleanliness and orderliness. For example, in my own company alone we have spent several hundred thousand dollars to separate operating equipment and functions, to provide a high degree of air filtration and dust control, and to insure the sanitation qualities of floors, ceilings and walls. This is typical of what the research-oriented companies are continuing to do to improve their operating areas.

Now I should like to point out a few fundamentals about manufacturing methods and procedures of the quality-minded drug manufacturer. Our equipment must fulfill two important requirements:

First, we must be able to produce batches of a drug product with uniform consistency day in and day out. Secondly, the equipment must be compatible with the chemicals involved and suitable for thorough cleaning to eliminate the possibility of contamination from product to product. Clearly, maintenance of equipment is extremely important. For example, in the case of a tablet compression machine, where close tolerances are required, regular examination is essential to insure that each tablet produced meets the dose specified. Such care is part of the standard operating procedure of the quality-conscious, innovator type of drug manufacturer.

All-important considerations for every reputable drug manufacturer are: (1) Quality of raw materials used in the manufacturing process and (2) In-process controls. I should like to elaborate on both of these points.

To assure the quality of a raw material, the careful company first insists that the supplier guarantee the quality and purity of the material, then makes doubly sure by conducting its own extensive tests. Many companies even conduct their own inspections of suppliers' plants.

This preoccupation with quality of raw materials applies to non-therapeutic as well as therapeutic substances; to non-official substances as well as those listed by the U.S. Pharmacopoeia and the National Formulary. In this connection, the following statement is made by one of these official compendia: "While one of the primary objects of the Pharmacopoeia is to assure the user of official medicinal substances of their identity, strength, quality and purity, it is manifestly impossible to include in each monograph a test for every impurity or adulterant that might be present". In view of this undisputed fact, the quality-oriented pharmaceutical firm exerts additional efforts through the use of analytical know-how and in-process controls to give greater assurance of the identity, strength, quality, and purity of the ingredients which go into its products.

Throughout the drug manufacturing process, from raw materials through finished product, careful control must be exercised at every step of the way. Every quality-minded manufacturer follows a standing operating procedure which incorporates a system of checks and balances followed by quality audits.

Included in these standard operations is a process for written procedures and specifications covering all raw materials and finished products. Items such as methods of sampling and analysis, and criteria for acceptance, are specified. All manufacturing formulas and working directions are as explicit as we can make them.

Our standard procedures cover such important considerations as product and container identity, quarantine provisions, and storage conditions. Each product is covered by an appropriate batch record, and throughout the manufacturing operation great care is exercised to assure accuracy of weight, volume, and yield of each batch.

Special care is exercised in the production of sterile products to avoid microbial contamination.

The packaging materials used are subjected to inspection, and particular care is exercised in the issuance of labels, cartons, and package inserts.

The warehousing of the finished product provides for proper storage, segregation, and identification by lot or batch number, as well as systematic rotation and inspection of stocks at regular intervals.