DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 15(6&7), 869-894 (1989)

QUALITY ASSURANCE

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INTRODUCTION

The total control of quality requires the organized effort of an entire company to assure the specified quality in each lot of drug product manufactured. The quality of oral solid dosage forms, as well as any drug dosage form, must be built in during plant construction, product research and development, purchasing of materials, production, testing, inspection, labeling, storage, and distribution. It cannot be assumed that end-product testing alone will ensure product quality.

Nearly all drug substances dispensed in the oral solid dosage form are stable under ordinary conditions. The essential qualities of a good compressed tablet are characterized by a number of specifications. These include the appearance, size, shape, thickness, weight, homogeneity, stability, hardness, dissolution time, and disintegration time. The appearance, size, shape, and thickness of the tablet are generally used to distinguish and identify the active ingredients which they contain. The remaining specifications assure the manufacturer that the tablets do not vary from allowable limits within the same lot or from one production lot to

another. All such qualities are designed to ensure a safe, therapeutically effective oral solid dosage form.

QUALITY ASSURANCE SYSTEM

Since manufacturing produces the tablets, they should have prime responsibility for quality results. Removal of the responsibility from manufacturing for producing a quality product results in lackluster product quality performance. Quality assurance, however, must establish control points to monitor the quality of the product as it is processed and on the final product. With experience, these control points are located at the critical points in the process flow. These include raw materials, in-process, complete processing, packaging line, finished product, and stability monitoring.

The quality assurance system is diagrammed in Figure 1. This system can vary in details, but not in principle, from company to company and will depend on the nature and size of the manufacturing facility and on the types of oral solid dosage form produced,

GOOD MANUFACTURING PRACTICES REQUIREMENTS

Most governments promulgate regulations governing the manufacture, processing, packaging, and distribution of finished pharmaceuticals. International standards have been published by the World Health Organization, but each country prefers to promulgate regulations that fit its own needs. Examples of such regulations in the United States are found in Part 211, Title 21 of the Code of Federal Regulations, "Current Good Manufacturing Practices in Manufacturing, Processing, Packaging, or Holding of Drugs" (CGMPs). These regulations were originally published in the Federal Register of June 20, 1963 by the Food and Drug Administration (FDA); and over the past 12 years these regulations have been revised several times. On February 13, 1976, the FDA

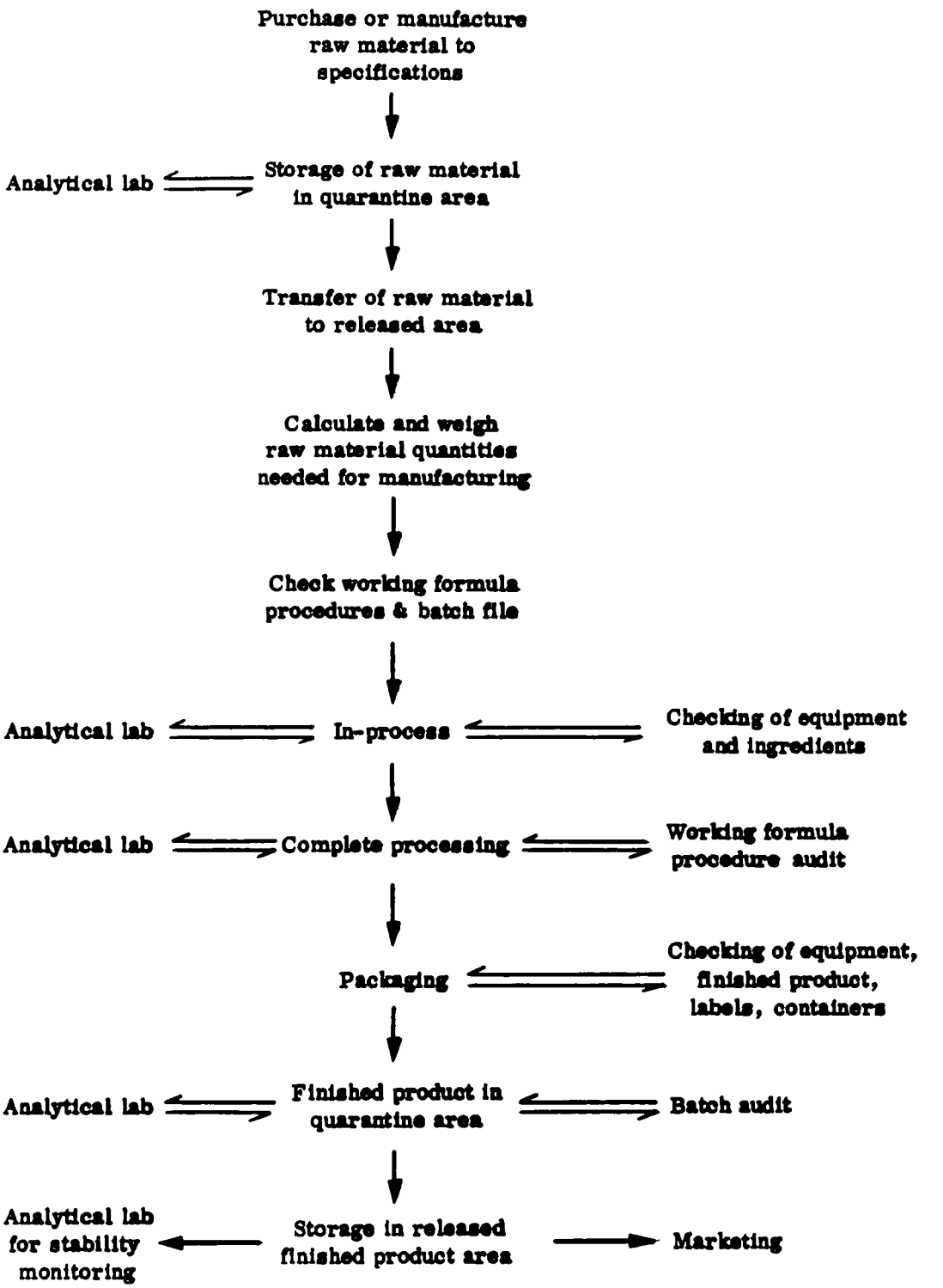

FIGURE 1

Quality Assurance System

published in the Federal Register proposals for revising drug CGMPs to update them in light of current technology and to adopt more specific requirements to better assure the quality of finished products. The final regulation was published in the Federal Register on March 28, 1979. The current CGMPs are enforced by the FDA it is on the basis of these regulations that the FDA has insisted on the proper manufacturing of drugs. The regulations extend into the area of finished pharmaceuticals, buildings, equipment, personnel, components, master production and control records, batch production, production and control procedures, product containers and their components, laboratory controls, distribution records, stability, expiration dating, and complaint files.

Regulations for good manufacturing practices during tablet manufacturing are aimed at assuring that only those tablets which have met the established specifications and are packed and labeled under proper controls are distributed.

COMPENDIAL REQUIREMENTS

Since the first officially recognized tablet appeared in the U.S. Pharmacopeia (USP IX) (1916), the number has steadily increased. Presently, the USP XXI and the National Formulary (NF) XVI officially recognizes 466 different tablets. Specifications published in the official compendia are designed to assure a pharmaceutically elegant and therapeutically effective dosage form. The acceptable limits of deviation are dependent upon the special problems associated with the production of the particular tablet. Individual monographs for tablets include tablet dosage-form uniformity by either weight variation or content uniformity, limits on disintegration time or dissolution besides the stated drug quantity. It is a compendial requirement that any sampling within a specific batch of tablets would reveal the tablets to be in compliance with respect to the individual monograph specifications.

A. Uniformity of Tablets Dosage Units

1. Weight Variation

2. Content Uniformity

B. Disintegration Time

C. Dissolution Test

RAW MATERIALS

The storage conditions of raw materials for tablets manufacturing, particularly hydroscopic substances, are important. Because of the great number of potential sources of contamination, strict sanitation of plant warehouse is an absolute necessity. Quality assurance should make periodic sanitation inspections and follow-up to assure that deficiencies are corrected.

An extensive and varied microbial flora is usually associated with raw materials from natural sources, for example gum arabic and tragacanth. Synthetic raw materials, on the other hand, are normally free or low in microbial contamination.

A. Sampling of Raw Materials

Samples of raw materials are to be collected in clean containers using a disinfected sampling "thief" or scoop, observing aseptic technique for microbiological analysis or clean container and clean technique for analytical laboratory. The number of containers to sample in a given lot can be determined by using MIL-STD-105D.

Samples are to be labeled as to lot number, receiving number, supplier, container size and type, name of raw material, and date of receipt. Samples are then submitted to quality assurance analytical and microbiological laboratories.

B. Chemical and Microbiological Attributes

In the development of raw material specifications, the analytic research and development chemist should strive for the following:

Ascertain which chemical, physical, and biological characteristics are critical for assuring reproducibility from lot to lot of raw materials to be used for evaluating each lot of raw material produced or purchased.

Establish the test methods and acceptable tolerance of the attributes to be evaluated.

Establish the supplier's ability to supply raw materials of consistent quality.

Good raw material spesifications must be written in precise terminology, be complete, and provide details of test methods, type of test instruments to use, manner of sampling, and proper identification. Figure 2 lists general tests, limits, and other physical or chemical data for raw materials related to identity, purity, strength, and manner of quality assurance.

The current FDA Good Manufacturing Practices (GMP) covering raw material handling procedures are found in the Code of Federal Regulations, Title 21, Section 211.42. It simply states that "components" be received, sampled, tested, and stored in a reasonable way, that rejected material be disposed of, that samples of tested components be retained, and that appropriate records of these steps be maintained. In practice, the manufacturer will physically inspect and assign lot numbers for all raw materials received and will quarantine them until they are approved for use. Each raw material is sampled according to standard sampling procedures and is sent to the quality control laboratory for testing according to the written procedures. If acceptable, it is moved to the release storage area and properly labeled to indicate the item number, name of material, lot number, date of release, reassay date, and signature of a quality assurance inspector. It is retested as necessary according to an established schedule to assure that it still conforms to specifications at time of use. Quality assurance should reserve samples from active and inactive raw materials required to determine whether the material meets the established specification. These reserve samples should be retained for at least 5 years. Approved compo-

A. (Raw Material Name)
   1. Structural formula, molecular weight
   2. Chemical name(s)
   3. Item number
   4. Date of issue
   5. Date of superseded, if any, or new
   6. Signature of writer
   7. Signature of approval

B. Samples
   1. Safety requirement
   2. Sample plan and procedure
   3. Sample size and sample container to be used
   4. Reservation sample required

C. Retest Program
   1. Retesting schedule
   2. Reanalysis to be performed to assure, identity, strength, quality, and purity

D. Specifications (wherever applicable)
   1. Description
   2. Solubility
   3. Identity
      a. specific chemical tests; organic nitrogenous basis; acid moiety or inorganic salt tests; sulfate, chloride, phosphate, sodium, and potassium; spot organic and inorganic chemical tests
      b. infrared absorption
      c. ultraviolet absorption
      d. melting range
      e. congealing point
      f. boiling point or range
      g. thin-layer, paper, liquid, or gas chromatography
   4. Purity and quality
      a. general completeness of solutions, pH, specific rotation, nonvolatile residue, ash, acid-insoluble ash, residue on ignition, loss on drying, water content, heavy metals, arsenic, lead, mercury, selenium, sulfate, chloride, carbonates, acid value, iodine value, saponification value
      b. special quality tests, particle size, crystallinity characteristics, and polymorphic forms
      c. special purity tests, ferric in ferrous salts, peroxides and aldehydes in ether and related degradation products
   5. Assay, calculated either on anhydrous or hydrous basis
   6. Microbial limits, especially for raw materials from natural sources

E. Test Procedures
   1. Compendial, USP, or NF references
   2. Noncompendial, detailed analytical procedure, weights; dilutions; extractions; normality; reagents; instrumentation used and procedure, if any; calculations

F. Approved Suppliers
   1. List of prime suppliers and other approved alternative suppliers, if any

FIGURE 2

Raw Material Quality Assurance Monograph

nents shall be rotated in such a manner that the oldest stock is used first. Any raw material not meeting specifications must be isolated from the acceptable materials, labeled as rejected, and returned to the supplier or disposed of promptly. To verify the supplier's conformance to specifications, further supporting assurance by means of on-site periodic inspections is pertinent to the total quality of raw materials. This will assure that cross-contamination does not take place due to improperly cleaned equipment or poor housekeeping practices since contaminants may go undetected because specifications generally are not designed to control the presence of unrelated materials. In general, raw materials may be classified into two basic groups: those that are active or therapeutic ingredients, and those that are inactive, inert materials.

ACTIVE OR THERAPEUTIC MATERIALS

A. Antibiotics

Antibiotics are one of the few drugs for which the official analytic method appears in the Code of Federal Regulations. The USP XXI and NF XVI refer to the Code of Federal Regulations for specifications and analytic methods given in the individual monographs for each antibiotic. The Code of Federal Regulations, Title 21, Chapter 1, Parts 436 to 436.517 and Parts 442 and 455, contains the analytic method specifications for all antibiotics approved for human use in the United States. The number of tests required varies from one antibiotic to another. Testing of antibiotic is generally performed by chemical, microbiological, or biological, methods, or by all three methods. Caution must be exercised during antibiotic raw material sampling for testing to assure that it is not altered during the sampling procedure. The sample must be taken in a relatively dry atmosphere, relatively free from dust, and free from both chemical and microbial airborne contamination, and exposure must be reduced to a minimum during sampling. Special attention should be given to the assay for

potency of antibiotic raw materials. Since the potency value in terms of micrograms per milligram obtained for this material is used in calculating the number of grams or kilograms required for the working formula procedures, it is recommended that at least two separate weighings of such antibiotic raw material powder be assayed on each of three different days (six different assays using six differing weighings). If all the individual results are not within the normal distribution of the group or show too much variance, additional assays should be done until a mean potency is obtained with confidence limits of ± 2.5% (or better) at P = 0.005

B. Actives Other than Antibiotics

The current editions of the USP XXI and NF XVI contain monographs on most therapeutically active materials used in tablet manufacturing. Since there is such a wide variance in the nature of the active ingredients used in tablet manufacturing, it is impossible to summarize briefly the testing of those raw materials. One of the must important decisions to be made in raw material control is the degree of purity that will be maintained for each material. It is not uncommon to find an appreciable variation in the degree of purity between samples of the same raw material purchased from different commercial sources. The selection then must be one which results in the highest purity practical for each raw material, consistent with safety and efficacy of the final oral dosage form. A typical raw material currently existing in a compendia has a purity requirement of generally not less than 97%. Its specifications normally consist of a description, solubility, idendification, melting range, loss on drying, residue on ignition, special metal testing, specific impurities that are pertinent to the method of synthesis of each individual raw material and assay. The methods of assay are usually chemical in nature. However, it should be indicated that these compendial tests are intended as the minimum required from the legal point of view. For certain tablet products, it may be necessary to obtain an

active ingredient with special specifications far tighter than those of the comparable compendial standard. Raw materials cannot be adequately evaluated and controlled withoud special instrumentation such as spectrophotometry; infrared spectrophotometry; potentiometric titrimetry; colomn, gas, paper, thin-layer, and high-pressure liquid chromatography; polarography; x-ray diffraction; x-ray fluorescence; spectrophotofluorimetry; calorimetry; and radioactive tracer techniques. No less demanding are the tests required for microbiological assay, pharmacological assay, and safety testing. For certain tablet products, even when highly purified and well-characterized raw materials are involved, specifications should include additional critical features such as particle size, crystal shape, and other peculiarities such as crystalline versus amorphous forms. Any of these characteristics could have an effect on the safety or effectiveness of the final oral dosage form. It is a GMP requirement that all raw materials, active or inactive, be assigned a reassay date, meaningful or indicative, that would assure purity and potency. Tests are performed at reassay times to confirm continued suitability of each raw material.

INACTIVE OR INERT MATERIALS

A. Diluent

B. Binders

C. Lubricants

D. Disintegrators

E. Coloring Agents

F. Flavoring Agents

G. Sweetening Agents

H. Coating Materials

CONTAINER

Compendium defines the container as that device that holds the drug and that is or may be in direct contact with the drug. The immediate container is that which is in direct contact with the drug at all times. The closure is a part of the container.

Container components should not interact physically or chemically with tablet product to alter the strength, quality, or purity beyond the specified requirements. The compendium provides specifications and test procedures for light resistance: well-closed, tight-closed, and four different types of glass containers.

Specifications and test methods are designed for containers on the basis of tests performed on the product in the container. The following features are to be considered in developing container specifications:

Properties of container tightness
Moisture and vapor tightness regardless of container construction
Toxicity, chemical, and physical characteristics of materials needed in container construction
Physical or chemical changes of container upon prolonged contact with tablet
Compatibility between container and tablet

Good Manufacturing Practices requires that stability date be submitted for any new drug substance for the finished dosage form of the drug in the container in which it is to be marketed.

The use of plastics in rigid containers, film and blister packs, especially in single-dosage containers, for tablet packaging has increased in the last 15 years. Obviously this is because of cost reduction in transportation and dispensing con-

venience. Plastics generally used in tablet packaging are polyethylenes, polypropylenes, cellulose plastics, polystyeene, and polyvinylchloride. Regardless of end use or fabrication method of polymer, additives must be compounded or dry-blended into the base resin. These additives can be classified as stabilizers, plasticizers, lubricants, colorants, fillers, impact modifiers, and processing aids. Not all polymers contain all of these types of additives. Polyethylene is one of the most thermally stable thermoplastics available. This means that polyethylene bottles ofter the best possible protection from breakage at an economical cost. This, along with other desirable processing and packaging properties, is the reason why high-density polyethylene (HDPE) is used for most tablet packaging in plastic bottles. The Pharmaceutical Manufacturers Association, the Society of the Plastics Industry and the USP prepared a monograph for polyethylene containers to be used for dry drug packaging. Tablets are protected from adverse moisture conditions, for example, vitamins and aspirin tablets, by the use of a tack seal adhesive. Generally a synthetic resin, emulsion-based material, such as formulated polyvinyl emulsion adhesive, is used. It should be noted that Good Manufacturing Practices classify packaging components, such as cartons, bottles, caps, film seal, adhesives, and labeling, as raw materials. Therefore, all previous quality assurance procedures for raw materials are to be followed for packaging components.

IN-PROCESS

Conformance to compendial standards as the sole basis for judging an oral dosage form to be perfectly satisfactory will be grossly misleading. Obviously, a compendial monograph could never cover all possibilities which might adversely affect the quality of a product. The difficulty lies in part in the fact that oral dosage forms are frequently produced in batches of hundred of thousands or even millions of tablets, so that the numbers of tablets assayed at the end of the process is not likely to represent more than a tiny fraction of the actual production.

There is a real and significant difference between a finished tablet product compendia standard and manufacturing quality assurance procedure. The CGMP guidelines emphasize environmental factors to minimize cross-contamination of products, labeling, and packaging errors, and the integrity of production and quality control records; but they do little to minimize within-batch and batch-to-batch variation in the output of production. Therefore, it is an important function of the in-process quality assurance program to ensure that tablets have uniform purity and quality within a batch and batch-to-batch.

BEFORE START CHECKING

A. Environmental Control and Sanitation

To assure that tablet dosage forms meet high standards of quality and purity, an effective sanitation program is required at all facilities where such products are manufactured. A successful extermination program must be enforced within and outside the plant to control insects and rodents. People are the mainstay of any plant housekeeping and sanitation program. Consequently, personal cleanliness, proper haircovering, clothing with appropriate pockets should be demanded. Floors, walls, and ceillings should be resistant to external forces, capable of being easily cleaned, and in good repair. Adequate ventilation, proper temperature, and proper humidity are other important factors. Ventilation in granulating, coating, and compression departments is usually designed such as to be able to absorb and remove dust. In such departmental operations, dust collectors, air filters, and scrubbers to clean the air are checked on a routine schedule. Air quality monitoring and foot candle measurements at the work station could be an indication of the adequacy of these elements.

The water supply may be potable or, distilled or, deionized and under adequate pressure to keep the water flowing clean. Deionization units should be checked and changed frequently to

deliver water of consistently high chemical and microbial quality as per written compendial or in-house specifications.

Quality assurance must review and check, based on written procedures that specify the details of the testing procedures and schedules, the following:

Sanitation
Cleaning records
Ventilation system: filter conditions and changes; pressure gage; humidity monitoring; temperature monitoring: microbial monitoring; light intensity, foot candle measurement
Water system: released sticker on point of use of water after checking and release from quality control laboratories; proper flushing period and/or volume before water use.

B. Manufacturing Working Formula Procedures (MWFPs)

Documentation of the component materials and processing steps, together with production operation specifications and equipment to be used, make up the MWFPs.

A working formula procedure should be prepared for each batch size that is produced. To attempt expansion or reduction of a batch size by manual calculations at the time of production cannot be considered good practice.

Quality assurance must review and check the working formula procedures for each production batch before, during, and after production operation for:

Signed and dated when issued by a responsible production person
Proper identification by name and dosage form, item number, lot number, effective date of document, and reference to a superseded version, if any, amount, lot, and code numbers of each raw material utilized
Each step initialed by two of the operators involved
Calculations of both active and inactive materials, especially if

there were any corrections for 100% potencies for actives used
Reassay dates of components used
Starting and finishing times of each operation
Equipment to be used and specification of its setup
Proper labeling of released components and equipment indicating product name, strength, lot number, and item number

C. Raw Materials

Quality assurance must check if any released raw material is to be taken to the production department in its original container; such containers should be cleaned. However, most raw materials are weighed in an environmental control weighing area where they are transferred to a secondary container that only circulates inside the production department. This secondary container should also be properly labeled with a sticker that bears all the information that was on the original container label. Only released raw materials with proper reassay dates are allowed in the production department. Raw materials intended for use in specific products should be stacked and isolated together with proper identification, name, dosage form, item number, lot number, weight, and signatures.

D. Manufacturing Equipment

Quality assurance must ensure that manufacturing equipment be designed, placed, and maintained in such a way as to facilitate thorough cleaning, be suitable for its intended use, and minimize any contamination of drugs and their containers during manufacture. Manufacturing equipment and utensils should be thoroughly cleaned and maintained in accordance with specific written directions. Whenever possible, equipment should be disassembled and thoroughly cleaned to preclude the carryover of drug residues from previous operations. Adequate records of such procedures and tests, if any, should be maintained by quality assurance. It is good manufacturing practice to use laboratory checks whenever possible to detect

trace quantities of drugs if products containing such drugs had been produced on a specific equipment.

Prior to the start of any production step, the quality assurance personnel should ascertain that the proper equipment and tooling for each manufacturing stage are being used. Equipment must be identified by labels bearing the name, dosage form, item number, and lot number. Equipment used for special batch production should be completely separated in the production department, and all dust-producing operations should be provided with adequate exhaust systems to prevent cross-contamination and recirculation of contaminated air.

Weighing and measuring equipment used in production and quality assurance, such as disintegration apparatus (unit and thermometer), friability testers, and balances, should be calibrated and checked at suitable intervals by appropriate methods; records of such tests should be maintained by quality assurance.

E. Sampling Procedure

Sampling procedures of finished tablet products can be based either on attribute inspection that grades the product as defective or nondefective or inspection by variables for percentage defective. The focal point of any sampling plan is the acceptable quality level (AQL). The second important step is to decide on the inspection level of the sampling plan, which will determine the relationship between the lot size and the sample size (N/n). The principle purpose of the sampling plan is to assure that tablets produced are of quality at least as good as the designated AQL. This means that as long as the fraction defective (r) is less than the AQL designated for a specific production procedure, then a large percentage of the lots of tablets produced will be accepted. Sampling procedures for inspection by variables for percentage defective may be used if a quality characteristic can be continuously measured and is known to be normally distributed, such as mean of the sample or the mean and standard deviation of the

sample. The assumption of a specific distributional form is a special feature of variable sampling. A separate plan must be employed for each quality characteristic that is being inspected or a common sampling plan is used, but the allowable number of defects varies for each quality characteristic; that is, no critical defects are allowed (c), but some minor defects are allowed. Also, the fraction defective vielded by a given process mean and standard deviation should be calculated to assure a normal distribution of sample statistics.

AFTER START CHECKING

A. Bulk Granulation and/or Raw Materials Processing

Only released, properly labeled raw materials are allowed in the granulation area. Depending upon the nature of the product, quality assurance should check and verify that the temperature and humidity in the area are within the specified limits required for the product. If the temperature and/or humidity is beyond the specified limits, production is to be informed and corrective actions must be taken.

The specified granulation procedure is to be checked,at each step in the process,according to written in-process quality assurance procedures.

Quality assurance should verify and document the proper equipment,the proper addition of ingredient,proper mixing time,proper drying time,and screening with proper mesh size sieves.

At certain points,samples are to be taken for the quality control laboratory for potency assay of the granulation and any other testing that is necessary to ensure batch uniformity.

Drums of in-process granulation or raw materials are labeled with product name,item number,lot number,gross,and tare are net weights of the contents.

B. Compression Processing

It is quality assurance's responsibility to ascertain that all drums of granulation or raw materials are properly labeled and

staged in the compression machine staging area, that they are clean, and that the compression machine is properly identified as to the product, strength, item number, and lot number.

The production process begins with the setup of the compression machine to prepare tablets within the specified limits for the particular product. Quality assurance at each step in the setup procedures verifies the addition of granulation and/or raw materials to the tablet press hopper and performs visual appearance, weight meassurement and hardness, friability, and disintegration tests as required to adjust the compression machine. Tablets produced during the compression machine setup period are rejected, accounted for, and destroyed.

A variable group of tests including tablet physical appearance, color, odor, thickness, diameter, friability, hardness, weight variation, and disintegration time are widely used for in-process tablet controls. Such in-process tests are designed to ensure control of problems that can arise during tablet granulation or when raw materials are compressed into tablets. These problems are distribution of active materials in the tablet, poor flow properties, cross-contamination, lamination or capping of tablets, faulty lubrication, higher or lower moisture content, high proportion of "powder".

In-process sampling plans will require a fast measuring method suited for testing single units. Weight, hardness, friability, and thickness can be measured rapidly. The Cahn Instrument Co. and the Mettler Instrument Corr. *have automatic balances that can operate in the weight range from below 1 to 10 g at about 50 tablets per minute, thus making single-tablet weighings easy and fast. By using such in-process automatic weighings, tablets from a full revolution of a multiple-punch compression machine with more than one hopper can be weighed in a few minutes to check for uniform punch performance and variance between left and right sides of the tablet machine.

* Cahn Instrument Company, California; Mettler Instrument Corp., New Jersey

Good Manufacturing Practices requires that in-process quality assurance be adequately documented throughout all stages of manufacturing. Throughout the compression run, in-process samples are removed, tested, and data recorded on special forms as specified in the product's in-process monograph. The number of samples taken for testing and the type of testing is obviously dependent upon the size of the batch and the type of product. If deviation from the specified limits occurs, the necessary corrective action is taken, recorded, and a resample is taken and tested to determine whether the quality attribute of the product is now within limits. In some instances, as in the case of compendial weight variation or disintegration time specifications, the deviation is such that all tablets produced prior to the corrective action are isolated, accounted for, and rejected. In some tablet compression machines, tablets are ejected from more than one side.
If this is the case, samples must be taken, tested, and recorded separately from all sides of the compression machine.

In addition to the above, portions of the initial, final, and in-process samples are used for collecting average run samples for the quality control laboratory for final batch analysis and release.

For antibiotic tablets, the Code of Federal Register specifies the number of samples and frequency of collection, for each individual antibiotic, that must be collected and sent to the Quality Control laboratory for testing and subsequent release of the batch.

There is no limit as to the ingenuity a quality assurance department can use in devising in-process control. The following sampling and testing schedule is often used for in-process quality assurance tablet production monitoring:

An initial and final sample is tested for physical appearance, tablet weight, thickness, diameter, hardness, friability, and disintegration.

An hourly sample for physical appearance testing.
Every second hour sample is tested for tablet friability, hardness, thickness, diameter, weight, and disintegration.

The homogeneity of the physical appearance of tablets is judged by visual examination and/or instrumentation. Speckled or mottled tablets indicate improper and incomplete blending resulting in uneven distribution of ingredients. Colors of compressed and coated tablets are usually compared to a reference standard. The surface of coated tablets is checked for smoothness before imprinting. In some cases, deterioration of some tablet ingredients may be gross and can be detected visually or by odor, such as acetic acid in hydrolyzed aspirin tablets.

A ±5% is usually allowed for tablet thickness, depending on the size of the tablet. Tablet thickness may vary from lot to lot due to the difference in density of the granulation, the pressure applied to the tablets, or the speed of the compression machine. Tablet thickness and diameter is important to ensure in filling equipment that uses tablet thickness as its counting mechanism. Tablet thickness is determined with a caliber as its thickness gauge in millimeters, for examples, Ames* thickness gauge.

Tablets must be fabricated to withstand chipping, abrasion, and breakage during the expected tablet life under conditions of storage, transportation, and handling. The hardness of a tablet is expressed as that force required to break the tablet. Hardness

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*Ames G., Division of Miles Laboratory Inc., Elkhart, Indiana
Schleuniger, Vicor Corp., Marion, Iowa
Pfizer Inc., New York, New York
Stokes, Division of Pennwalt Corp., Warminster, Pennsylvania
Roche Laboratories, Division of Hoffman-LaRoche Inc., Nutley, New Jersey

can be measured by the Schleuniger* (Strong Cobb), Pfizer*, and the Stokes* Hardness Testers. The hardness values of the Strong Cobb is not equivalent to the Pfizer or the Stokes instrument. A maximum breaking load of four Strong Cobb units or equivalent is essential in order to ensure sufficient hardness. Exceptionally soft tablets may not withstand handling, while excessively hard tablets may chip or fracture or not disintegrate in the required period of time.

The Roche* Friabilator represents a device to determine tablet friability. The instruments are designed to measure the wearing qualities of tablets. A number of tablets are weighed and placed in the tumbling apparatus. After a given number of rotations, the tablets are weighed; and the loss in weight is a measure of the ability of the tablets to withstand this type of wear.

Actually, it is a common practice to trial-ship tablets using different methods of transportation to check the tablet's ability to withstand transportation handling.

The use of control charts is increasingly becoming an essential part of any quality assurance operation. Control charts may be classified as attributes or variable types. Variable charts are based on the normal distribution of actual numerical measurements of quality attributes, while attribute charts refer to some other attributes of quality that are present or absent in which each sample inspecter is tested to determine if it conforms to the requirements. Variable charts, or the X, R (mean and range) charts, are undoubtedly the most generally used charts in quality assurance of tablets. The most common and usual application of variable charts in tablet manufacture is in hardness and weight control. Routinely, in-process results are plotted on a control chart so that a complete picture of any possible fluctuation during the entire compression operation can be readily detected. The control limits or process capability can be determined by sampling, measuring, and recording weights in subgroups that cover the compression operation. The range within each subgroup, that is, the

absolute number difference between the lowest and highest individual tablet reading, and the average number difference between the lowest and highest individual tablet reading, and the average range are calculated for the total number of groups. The average tablet-reading plots can detect movements towards limits that will allow making necessary corrections before limit values are exceeded. While the subgroup's sample range plots will allow the monitoring of the sample range trend, an increase in sample range values or general high variability indicates possible control problems.

When the tablet-manufacturing process has been completed, the theoretical yields to be expected from the formulation at different stages of manufacture and the accountability calculations are checked for comparison with the practical and the permissible yield limits. Such information is recorded on appropriate forms and any discrepancy must be reconciled if beyond process allowable variation.

FINISHED PRODUCT

A. Specification

Final testing of tablets is made in the quality control laboratories. These tests are designed to determine compliance with specifications. Thus, the testing of the finished product for compliance with predetermined standards prior to release of the tablets for packaging and subsequent distribution is a critical factor for quality assurance. The purpose of establishing these specifications and standarts is to ensure that each tablet contains the amount of drug claimed on the label, that all of the drug in each tablet is available for complete absorption, that the drug is stable in the formulation in its specific final container for its expected shelf life, and that the tablets themselves contain no toxic foreign substances. Normally, the design of test param-

Table 1

Quality Control Physical, Chemical, and Microbial Attributes for the Evaluation of Tablets

1. Appearance, odor, color, taste
2. Hardness
3. Disintegration
4. Friability
5. Thickness uniformity
6. Weight uniformity
7. Assay of the active ingredient
8. Moisture content
9. Light stability
10. Identification tests for the active ingredient and possible contaminants
11. Content uniformity
12. Dissolution
13. Microbial limits, e.g., total microbial count
14. Stability of the active ingredient in the formula and marketed container

eters, procedure, and specifications are done during product development. It is a good manufacturing practice to base such parameters on experiences developed from several pilot and production batches. Furthermore, the results of these studies should be subjected to statistical analysis in order to correctly appraise the precision and accuracy of each procedure for each characteristic. In the long run, with additional production experience it is possible that specifications be modified for perfection and upgrade of product specifications. The complexity of quality control testing of tablets can be clearly understood from the quality control attributes outlined in Table 1.

B. Bulk Tablets Testing

Each lot of tablets should be tested to ensure identity, quality, potency, and purity. Quality assurance will authorize the release for further processing based on actual laboratory testing: physical, chemical, and/or biological.

Tests required by the official compendia on the ingredients and the dosage form applies to all manufacturers of a specific compendia tablet product. The manufacturer frequently employs alternative methods that are more accurate, specific, or economical than those in the compendia.

The manufacturer is not required to employ the official analytical procedures as long as the quality of his product complies with the compendium requirements. However, in the case of a legal action, the compendium procedures are the basis for determining compliance.

C. Quality Assurance During Packaging Operation

If the quality control laboratory analysis confirms that the product complies with specifications and quality assurance audit of manufacturing operations are satisfactory, the bulk tablet product is released to the packaging department and production control is notified. Production control issues a packaging form which carries the name of the tablet product, item number, lot number, number of labels, inserts, packaging materials to be used, operations to be performed, and the quantity to be packaged. A copy of this form is sent to the supervisor of label control, which in turn will count out the required number of labels. Since labels may be spoiled during the packaging operation, a definite number in excess of that actually required is usually issued. However, all labels must be accounted for before its destruction. If the lot number and expiration date of the tablets product are not going to be printed directly on the line, the labels are run through a printing machine which imprints the lot number and expiration date. The labels are recounted and placed in a separate container with

proper identification for future transfer to the packaging department. The packaging department then requests, according to the packaging form, the product to be packaged and all packaging components, such as labels, inserts, bottles, caps, seals, cartons, and shipping cases. Quality assurance inspects and verifies all packaging components, equipment to be used for the packaging operation to ensure that it has the proper identification and the line has been thoroughly cleaned and that all materials from the previous packaging operation have been completely removed. Packaging operations should be performed with adequate physical segregation from product to product. Tablets of similar shape should not be scheduled on the neighboring packaging lines at the same time. Quality assurance should periodically inspect the packaging line and check filled and labeled containers for compliance with written specification, for example, absence of goreign drugs and labels, adequacy of the containers and closure system, and accuracy of labeling. Some packaging operations, especially those using high-speed equipments, are fitted with automated testing equipment to check each container for fill and label placement. Alternatively, an operator may visually inspect all packages fed into the final cartons. Proper reconciliation and disposition of the unused and wasted labels should occur at the end of the packaging operation. Quality assurance should select finished preservation samples at random from each lot. The preservation samples should consist of at least twice the quantity necessary to perform all tests required to determine whether the product meets its established specifications. These preservation samples should be retained for at least 2 years after the expiration date and stored in their original package under conditions consistent with product labeling.

Quality assurance should also select a finished sample and send it to the analytical control laboratory for final testing, which is usually an identification test.

D. Auditing

Good Manufacturing Pratice requires that the manufacturing process be adequately documented throughout all stages of the

operation. The history of each task from the starting materials, equipment used, personnel involved in production and control until completed packaging is complete, should be recorded. Preservation samples are to be stored for at least 2 years beyond the labeled expiration date of each product. The areas of record keeping are:

Individual components, raw materials, and packaging
Master formula
Batch production
Container and labeling
Packaging and labeling operation
Laboratory control testing, in-process and finished
Proper signing and dating by at least two individuals independently for each operation in the proper spaces
Reconciliation of materials supplied with amount of tablets proced, taking into account allowable loss limits

Before releasing the product for distribution, quality assurance should evaluate the batch records of all in-process tests and controls and all tests of the final product to determine whether they conform to specification.