Inspections, Compliance, Enforcement, and Criminal Investigations

Dosage Form Drug Manufacturers cGMPs (10/93)

GUIDE TO INSPECTIONS OF DOSAGE FORM DRUG MANUFACTURER'S - CGMPR'S

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I. INTRODUCTION

This document is intended to be a general guide to inspections of drug manufacturers to determine their compliance with the drug CGMPR's. This guide should be used with instructions in the IOM, other drug inspection guides, and compliance programs. A list of the inspection guides is referenced in Chapter 10 of the IOM. Some of these guides are:

o Guide to Inspections of Bulk Pharmaceutical Chemicals.

o Guide to Inspections of High Purity Water Systems.

o Guide to Inspections of Pharmaceutical Quality Control Laboratories.

o Guide to Inspections of Microbiological Pharmaceutical Quality Control Laboratories.

o Guide to Inspections of Lyophilization of Parenterals.

o Guide to Inspections of Validation of Cleaning Processes.

o Guide to Inspections of Computerized Systems in Drug Processing.

o Guideline on General Principles of Process Validation.

II. CURRENT GOOD

MANUFACTURING PRACTICE

REGULATIONS

Prescription vs. Non-prescription

All drugs must be manufactured in accordance with the current good manufacturing practice regulations

otherwise they are considered to be adulterated within the meaning of the FD&C Act, Section 501(a)(2)(B) Records relating to prescription drugs must be readily available for review in accordance with Sec. 704(a)(1)(B) of the FD&C Act. If the product is an OTC drug which is covered by an NDA or ANDA, FDA may review, copy and verify the records under Sec. 505(k)(2) of the FD&C Act. However, if the product is an OTC drug for which there is no application filed with FDA, the firm is not legally required to show these records to the investigator during an inspection being conducted under Section 704 of the FD&C Act. Nonetheless, all manufacturers of prescription and OTC drugs must comply with the drug CGMPR requirements, including those involving records. The investigator should review these records as part of the inspection in determining the firm's compliance with the CGMP regulations. On rare occasions, a firm may refuse to allow review of OTC records stating they are not legally required to. While the firm may be under no legal obligation to permit review of such records, this does not relieve the firm of its statutory requirement to comply with the good manufacturing practices under section 501(a)(2)(B) of the Food Drug and Cosmetic Act, including the requirements for maintaining records.

If a firm refuses review of OTC records, the investigator should determine by other inspectional means the extent of the firm's compliance with CGMPR's. Inspectional observations and findings that CGMPR's are not being followed are to be cited on a List of Inspectional Observations, FDA-483, for both prescription and non-prescription drugs.

Organization and Personnel [21 CFR 211 Subpart B]

The firm must have a quality control department that has the responsibility and authority as described in the referenced CFR. The quality control department must maintain its independence from the production department, and its responsibilities must be in writing.

Obtain the name, title and individual responsibilities of corporate officers and other key employees as indicated in the IOM.

In the drug industry, an employee's education and training for their position has a significant impact on the production of a quality product. Report whether the firm has a formalized training program, and describe the type of training received. The training received by an employee should be documented.

Quality control must do product annual review on each drug manufactured, and have written annual review procedures. Review these reports in detail. This report will quickly let you know if the manufacturing process is under control. The report should provide a summary all lots that failed in-process or finished product testing, and other critical factors. Investigate any failures.

Quality control must validate the manufacturing process for each drug manufactured. Review and evaluate this data.

Buildings and Facilities [21 CFR 211 Subpart C]

Review the construction, size, and location of plant in relation to surroundings. There must be adequate lighting, ventilation, screening, and proper physical barriers for all operations including dust, temperature, humidity, and bacteriological controls. There must be adequate blueprints which describe the high purity water, HEPA, and compressed air systems. The site must have adequate locker, toilet, and hand washing facilities.

The firm must provide adequate space for the placement of equipment and materials to prevent mix-ups in the following operations:

o receiving, sampling, and storage of raw materials;

o manufacturing or processing;

o packaging and labeling;

o storage for containers, packaging materials, labeling, and finished products;

o production and control laboratories.

Equipment [21 CFR 211 Subpart D]

Review the design, capacity, construction, and location of equipment used in the manufacturing, processing, packaging, labeling, and laboratories. Describe the manufacturing equipment including brief descriptions of operating principles. Consider the use of photographs, flow charts, and diagrams to supplement written descriptions.

New equipment must be properly installed, and operate as designed. Determine if the equipment change would require FDA pre-approval and/or revalidation of the manufacturing process. The equipment must be cleaned before use according to written procedures. The cleaning must be documented and validated.

The equipment should not adversely effect the identity, strength, quality, or purity of the drug. The material used to manufacture the equipment must not react with the drug. Also, lubricants or coolants mus not contaminate the drug.

The equipment should be constructed and located to ease cleaning, adjustments, and maintenance. Also, it should prevent contamination from other or previous manufacturing operations. Equipment must be identified as to its cleaning status and content. The cleaning and maintenance of the equipment are usually documented in a log book maintained in the immediate area. Determine if the equipment is of suitable capacity and accuracy for use in measuring, weighing, or mixing operations. If the equipment requires calibration, they must have a written procedure for calibrating the equipment and document the calibration

Components and Product Containers [21 CFR 211 Subpart E]

Inspect the warehouse and determine how components, drug product containers, and closures are received, identified, stored, handled, sampled, tested, and approved or rejected. They must have written procedures which describe how these operations are done. Challenge the system to decide if it is functioning correctly. If the handling and storage of components are computer controlled, the program mus be validated.

The receiving records must provide traceability to the component manufacturer and supplier. The receiving records for components should contain the name of the component, manufacturer, supplier if different from the manufacturer, and carrier. In addition, it should include the receiving date, manufacturer's lot number, quantity received, and control number assigned by the firm.

Check sanitary conditions in the storage area, stock rotation practices, retest dates, and special storage conditions (protection from light, moisture, temperature, air, etc.). Inspect glandular and botanical components for insect infestation.

Components or finished product adulterated by rodents, insects, or chemicals must be documented and submitted for seizure.

Collect the evidence even if the firm plans to voluntarily destroy the product. Be alert for components, colors, and food additives that may be new drug substances, appear to have no use in the plant or appear to be from an unknown supplier. Check the colors against the Color Additives Status List in the IOM Determine if the color is approved for its intended use, and required statements are declared on the drug label.

Components might be received at more than one location. Components must be handled in accordance with the drug CGMP's including components used in the research and development lab. Determine how components are identified after receipt and quarantined until released. Components must be identified so the status (quarantine, approved, or rejected) is known. Review the criteria for removing components from quarantine and challenge the system. Determine what records are maintained in the storage area to document the movement of components to other areas, and how rejected components handled. The component container has an identification code affixed to it. This unique code provides traceability from the component manufacturer to its use in the finished product.

Review the sampling and testing procedures for components, and the process by which approved materials are released for use. Decide if these practices are adequate and followed.

Determine the validity, and accuracy of the firm's inventory system for drug components, containers, closures and labeling. Challenge the component inventory records by weighing a lot and comparing the results against the quantity remaining on the inventory record. Significant discrepancies in these records should be investigated.

Evaluate the following to determine whether the firm has shown that the containers and closures are compatible with the product, will provide adequate protection for the drug against deterioration or contamination, are not additive or absorptive, and are suitable for use:

o Specifications for containers, closures, cotton filler, and desiccant, etc.

o What tests or checks are made (cracks, glass particles, durability of material, metal particles in ointment tubes, compliance with compendium specifications, etc.).

o Cleaning procedures and how containers are stored.

o Handling of preprinted containers. Are these controlled as labeling, or as containers? The firm must review the labeling for accuracy.

Production and Process Controls [21 CFR Subpart F]

1. Critical Manufacturing Steps [21 CFR 211.101]

Each critical step in the manufacturing process shall be done by a responsible individual and checked by a second responsible individual. If such steps in the processing are controlled by automatic mechanical or electronic equipment, its performance should be verified.

Critical manufacturing steps include the selection, weighing, measuring and identifying of components, and

addition of components during processing. It includes the recording of deviations from the batch record, mixing time and testing of in-process material, and the determination of actual yield and percent of theoretical yield. These manufacturing steps are documented when done, and not before or after the fact.

2. Equipment Identification [21 CFR 211.105]

All containers and equipment used in to manufacture a drug should be labeled at all times. The label should identify the contents of the container or equipment including the batch number, and stage of processing. Previous identification labels should be removed. The batch should be handled and stored to prevent mixups or contamination.

3. In-Line and Bulk Testing [21 CFR 211.110]

To ensure the uniformity and integrity of products, there shall be adequate in-process controls, such as checking the weights and disintegration time of tablets, the fill of liquids, the adequacy of mixing, the homogeneity of suspensions, and the clarity of solutions.

Determine if in-process test equipment is on site and the specified tests are done. Be alert for prerecording of test results such as tablet weight determinations.

The bulk drug is usually held in quarantine until all tests are completed before it is released to the packagin and labeling department. However, the testing might be done after packaging. product.

4. Actual Yield [21 CFR 211.103]

Determine if personnel check the actual against the theoretical yield of each batch of drug manufactured. In the event of any significant unexplained discrepancies, determine if there is a procedure to prevent distribution of the batch in question, and related batches.

5. Personnel Habits

Observe the work habits of plant personnel. Determine:

Their attitudes and actions involving the jobs they perform. (Careless, lackadaisical, disgruntled, etc.).

Their dress. (Clean dresses, coats, shirts and pants, head coverings, etc.

If proper equipment is used for a given job or whether short cuts are taken (i.e. use of hands and arms to mix or empty trays of drug components).

If there are significant written or verbal language barriers that could affect their job performance.

Tablet and Capsule Products

Become familiar with the type of equipment and its location in the tableting operation. The equipment may include rotary tableting machines, coating and polishing pans, punches and dies, etc. The equipment should be constructed and located to facilitate maintenance and cleaning at the end of each batch or at suitable

intervals in the case of a continuous batch operation. If possible, observe the cleaning and determine if the cleaning procedure is followed.

The ingredients in a tablet are the active ingredient, binders, disintegrators, bases, and lubricants. The binder is added to the batch to keep the tablet together. Excess binder will make the tablet too hard for use. The disintegrator is used to help disintegration of the tablet after administration. The base should be an inert substance which is compatible with the active ingredient and is added to provide size and weight. The lubricant helps in the flow of granulated material, prevents adhesion of the tablet material to the surface of punches and dies, and helps in tablet ejection from the machine.

Tablets and capsules are susceptible to airborne contamination because of the manipulation of large quantities of dry ingredients. To prevent cross-contamination in the tableting department, pay close attention to the maintenance, cleaning, and location of equipment, and the storage of granulations and tablets. To prevent cross-contamination, the mixing, granulation, drying and/or tableting operation should be segregated in enclosed areas with its own air handling system. Determine what precautions are taken to prevent cross-contamination. When cross-contamination is suspect, investigate the problem and collect in-line samples(INV) and official samples of the suspect product. Determine what temperature, humidity, and dust collecting controls are used by the firm in manufacturing operations. Lack of temperature and humidity controls can affect the quality of the tablet.

Observe the actual operation of the equipment and determine whether powders or granulations are processed according to the firm's specifications. The mixing process must be validated. The drying ovens should have their own air handling system which will prevent cross-contamination. Does the firm record drying time/temperature and maintain recording charts including loss on drying test results? Review the in-line tests performed by production and/or quality control. Some in-process tests are tablet weight, thickness, hardness, disintegration , and friability. Evaluate the disposition of in-process samples.

Capsules may be either hard, or soft type. They are filled with powder, beads, or liquid by machine. The manufacturing operation of powders for capsules should follow the same practice as for tablets. Determine manufacturing controls used, in-line testing, and basis for evaluating test results for the filling operations.

Sterile Products

Typically, a sterile drug contains no viable microorganisms and is non-pyrogenic. Drugs for intravenous injection, irrigation, and as ophthalmic preparations, etc., meet this criteria. In addition, other dosage forms might be labeled as sterile. For instance, an ointment applied to a puncture wound or skin abrasion.

Parenteral drugs must be non-pyrogenic, because the presence of pyrogens can cause a febrile reaction in human beings. Pyrogens are the products of the growth of microorganisms. Therefore, any condition that permits bacterial growth should be avoided in the manufacturing process. Pyrogens may develop in water located in stills, storage tanks, dead legs, and piping, or from surface contamination of containers, closures or other equipment. Parenterals may also contain chemical contaminants that will produce a pyretic response in humans or animals although there are no pyrogens present.

There are many excellent reference materials which should be reviewed before the inspection. Some of these are the "Guideline on Sterile Drug Products Produced by Aseptic Processing," and chapter 84 on pyrogens in the Remington's Pharmaceutical Sciences.

Determine and evaluate the procedures used to minimize the hazard of contamination with microorganisms and particulates of sterile drugs.

o Personnel

Review the training program to ensure that personnel performing production and control procedures have experience and training commensurate with their intended duties. It is important that personnel be trained in aseptic procedures. The employees must be properly gowned and use good aseptic techniques.

o Buildings

The non-sterile preparation areas for sterile drugs should be controlled. Refer to Subpart C of the proposed CGMPR's for LVP's; however, deviations from these proposed regulations are not necessarily deviations from the CGMPR's. Evaluate the air cleanliness classification of the area. For guidance in this area, review Federal Standard #209E entitled "Airborne Particulate Cleanliness Classes in Cleanrooms and Clean Zones." Observe the formulation practices or procedures used in the preparation areas. Be alert for routes of contamination. Determine how the firm minimizes traffic and unnecessary activity in the preparation area. Determine if filling rooms and other aseptic areas are constructed to eliminate possible areas for microbiological/particulate contamination. For instance, dust-collecting ledges, porous surfaces, etc. Determine how aseptic areas are cleaned and maintained.

1. Air

Air supplied to the non-sterile preparation or formulation area for manufacturing solutions prior to sterilization should be filtered as necessary to control particulates. Air being supplied to product exposure areas where sterile drugs are processed and handled should be high efficiency particulate air (HEPA) filtered under positive pressure.

Review the firm's system for HEPA filters, determine if they are certified and/or Dioctyl Phthalate (DOP) tested and frequency of testing.

Review the compressed air system and determine if it is filtered at the point of use to control particulates. Diagrams of the HEPA filtered and compressed air systems should be reviewed and evaluated.

2. Environmental Controls

Specifications for viable and non-viable particulates must be established. Specifications for viable particulates must include provisions for both air and surface sampling of aseptic processing areas and equipment. Review the firm's environmental control program, specifications, and test data. Determine if the firm follows its procedure for reviewing out-of-limit test results. Also, determine if review of environmental test data is included as a part of the firm's release procedures.

Note: In the preparation of media for environmental air and surface sampling, suitable inactivating agents should be added. For example, the addition of penicillinase to media used for monitoring sterile penicillin operations and cephalosporin products.

o Equipment

Determine how the equipment operates including the cleaning and maintenance practices. Determine how equipment used in the filling room is sterilized, and if the sterilization cycle has been validated. Determine the practice of re-sterilizing equipment if sterility has been compromised.

Determine the type of filters used. Determine the purpose of the filters, how they are assembled, cleaned, and inspected for damage. Determine if a microbial retentive filter, and integrity testing is required.

o Water for Injection

Water used in the production of sterile drugs must be controlled to assure that it meets U.S.P. specifications. Review the firm's water for injection production, storage, and delivery system. Determine that the stills, filters, storage tanks, and pipes are installed and operated in a manner that will not contaminate the water. Evaluate the firm's procedures and specifications that assure the quality of the water for injection. As reference material, review the "FDA Guide to Inspecteons of High Purity Water Systems" before initiating an inspection.

o Containers and Closures

Determine how containers and closures are handled and stored. Decide if the cleaning, sterilization, and depyrogenization are adequate, and have been validated.

o Sterilization

1. Methods

Determine what method of sterilization is used. A good source of reference material on validation of various sterilization processes is the Parenteral Drug Association Technical Reports. For instance, Technical Report #1 covers "Validation of Steam Sterilization Cycles." Review and evaluate the validation data whatever the method employed.

If steam under pressure is used, an essential control is a mercury thermometer and a recording thermomete installed in the exhaust line. The time required to heat the center of the largest container to the desired temperature must be known. Steam must expel all air from the sterilizer chamber to eliminate cold spots. The drain lines should be connected to the sewer by means of an air break to prevent back siphoning. The use of paper layers or liners and other practices which might block the flow of steam should be avoided. Charts of time, temperature, and pressure should be filed for each sterilizer load.

If sterile filtration is used, determine the firm's criteria for selecting the filter and the frequency of changing Review the filter validation data. Determine if the firm knows the bioburden of the drug, and examine their procedures for filter integrity testing. Filters might not be changed after each batch is sterilized. Determine if there is data to justify the integrity of the filters for the time used and that "grow through" has not occurred.

If ethylene oxide sterilization is used, determine what tests are made for residues and degradation. Review the ETO sterilization cycle including preconditioning of the product, ETO concentration, gas exposure time, chamber and product temperature, and chamber humidity.

2. Indicators

Determine the type of indicator used to assure sterility. Such as, lag thermometers, peak controls, Steam Klox, test cultures, biological indicators, etc.

Caution: When spore test strips are used to test the effectiveness of ethylene oxide sterilization, be aware that refrigeration may cause condensation on removal to room temperature. Moisture on the strips converts the spore to the more susceptible vegetative forms of the organism which may affect the reliability of the

sterilization test. The spore strips should not be stored where they could be exposed to low levels of ethylene oxide.

If biological indicators are used, review the current U.S.P. on sterilization and biological indicators. In some cases, testing biological indicators may become all or part of the sterility testing.

Biological indicators are of two forms, each of which incorporates a viable culture of a single species of microorganism. In one form, the culture is added to representative units of the lot to be sterilized or to a simulated product that offers no less resistance to sterilization than the product to be sterilized. The second form is used when the first form is not practical as in the case of solids. In the second form, the culture is added to disks or strips of filter paper, or metal, glass, or plastic beads.

During the inspection of a firm which relies on biological indicators, review background data complied by the firm to include:

o Surveys of the types and numbers of organisms in the product before sterilization.

o Data on the resistance of the organism to the specific sterilization process.

o Data used for selecting the most resistant organism and its form (spore or vegetative cell).

o Studies of the stability and resistance of the selected organism to the specific sterilization process.

o Studies on the recovery of the organism used to inoculate the product.

o If a simulated product or surface similar to the solid product is used, validation of the simulation or similarity. The simulated product or similar surface must not affect the recovery of the numbers of indicator organisms applied.

o Validation of the number of organisms used to inoculate the product, simulated product, or similar surface to include stability of the inoculum during the sterilization process.

Since qualified personnel are crucial to the selection and application of these indicators, review their qualifications including experience dealing with the process, expected contaminants, testing of resistance of organisms, and technique.

Review the firm's instructions regarding use, control and testing, of the biological indicator by product including a description of the method used to demonstrate presence or absence of viable indicator in or on the product.

Review the data used to support the use of the indicator each time it is used. Include the counts of the inoculum used; recovery data to control the method used to demonstrate the sterilization of the indicator organism; counts on unprocessed, inoculated material to

indicate the stability of the inoculum for the process time; and

results of sterility testing specifically designed to demonstrate the presence or absence of the indicator organism for each batch or filling operation.

In using indicators, you must assure yourself that the organisms are handled so they don't contaminate the drug manufacturing area and product.

3. Filled Containers

Evaluate how the filled vials or ampules leave the filling room. Is the capping or sealing done in the sterile fi area? If not, how is sterility maintained until capped?

Review the tests done on finished vials, ampules, or other containers, to assure proper fill and seal. For instance, leak and torque tests.

Review examinations made for particulcte contamination. You can quickly check for suspected particulate matter by using a polariscope. Employees doing visual examinations on line must be properly trained. If particle counts are done by machine, this operation must be validated.

4. Personnel Practices

Check how the employees sterilize and operate the equipment used in the filling area.

Observe filling room personnel practices. Are the employees properly dressed in sterile gowns, masks, caps, and shoe coverings? Observe and evaluate the gowning procedures, and determine if good aseptic technique is maintained in the dressing and filling rooms.

Check on the practices after lunch and other absences. Is fresh sterile garb supplied, or are soiled garment reused?

Determine if the dressing room is next to the filling area and how employees and supplies enter the sterile area.

o Laboratory Controls

For guidance on how to inspect micro and chemistry labs, review the "FDA Guide to Inspections of Pharmaceutical Quality Control Laboratories" and "FDA Guide to Inspections of Microbiological Pharmaceutical Quality Control Laboratories."

1. Retesting for Sterility

See the USP for guidance on sterility testing. Sterility retesting is acceptable provided the cause of the initial non-sterility is known, and thereby invalidates the original results. It cannot be assumed that the initial sterility test failure is a false positive. This conclusion must be justified by sufficient documented investigation. Additionally, spotty or low level contamination may not be identified by repeated sampling an testing.

Review sterility test failures and determine the incidence, procedures for handling, and final disposition of the batches involved.

2. Retesting for Pyrogens

As with sterility, pyrogen retesting can be performed provided it is known that the test system was compromised. It cannot be assumed that the failure is a false positive without documented justification.

Review any initial pyrogen test failures and determine the firm's justification for retesting.

3. Particulate Matter Testing

Particulate matter consists of extraneous, mobile, undissolved substances, other than gas bubbles, unintentionally present in parenteral solutions.

Cleanliness specifications or levels of non-viable particulate contamination must be established. Limits are usually based on the history of the process. The particulate matter test procedure and limits for LVP's in the U.S.P. can be used as a general guideline. However, the levels of particulate contamination in sterile powders are generally greater than in LVP's. LVP solutions are filtered during the filling operation. However, sterile powders, except powders lyophilized in vials, cannot include filtration as a part of the filling operation. Considerable particulate contamination is also present in sterile powders which are spray dried due to charring during the process.

Review the particulate matter test procedure and release criteria. Review production and control records of any batches for which complaints of particulate matter have been received.

o Production Records

Production records should be similar to those for other dosage forms. Critical steps, such as integrity testing of filters, should be signed and dated by a second responsible person.

Review production records to ensure that directions for significant manufacturing steps are included and reflect a complete history of production.

Ointments, Liquids, and Lotions

Major factors in the preparation of these drugs are the selection of raw materials, manufacturing practices, equipment, controls, and laboratory testing.

Following the basic drug inspection fundamentals, fully evaluate the production procedures. In addition, evaluate specific information regarding:

o The selection and compatibility of ingredients.

o Whether the drug is a homogeneous preparation free of extraneous matter.

o The possibility of decomposition, separation, or crystallization of ingredients.

o The adequacy of ultimate containers to hold and dispense contents.

o Procedure for cleaning the containers before filling.

o Maintenance of homogeneity during manufacturing and filling operations.

The most common problem associated with the production of these dosage forms is microbiological contamination caused by faulty design and/or control of purified water systems. During inspections, evaluate the adequacy of the water system. Review and evaluate the micro/chemistry test results on the routine monitoring of the water system including validation of the water system. Review any microbiological tests done on the finished drug including in-process testing.

Some of these drugs have preservatives added which protect them from microbial contamination. The preservatives are used primarily in multiple-dose containers to inhibit the growth of microorganisms introduced inadvertently during or after manufacturing. Evaluate the adequacy of preservative system. Preservative effectiveness testing for these products should be reviewed. For additional information, review the "Antimicrobial Preservatives-Effectiveness" section of the U.S.P..

Equipment employed for manufacturing topical drugs is sometimes difficult to clean. This is especially true for those which contain insoluble active ingredients, such as the sulfa drugs. The firm's equipment cleaning procedures including cleaning validation data should be reviewed and evaluated.

Packaging and Labeling [21 CFR Subpart G]

Packaging and labeling operations must be controlled so only those drugs which meet the specifications established in the master formula records are distributed. Review in detail the packaging and labeling operations to decide if the system will prevent drug and label mix-ups. Approximately 25% of all drug recalls originate in this area.

Evaluate what controls or procedures the firm has to provide positive assurance that all labels are correct. Determine if packaging and labeling operations include:

o Adequate physical separation of labeling and packaging operations from manufacturing process.

o Review of:

1. Label copy before delivery to the printer.

2. Printer's copy.

3. Whether firm's representative inspects the printer.

4. Whether or not gang printing is prohibited.

5. Whether labels are checked against the master label before released to stock. Determine who is responsible for label review prior to release of the labels to production. Also, whether the labels are identical to the labeling specified in the batch production records.

o Separate storage of each label (including package inserts) to avoid mixups.

o Inventory of label stocks. Determine if the printer's count is accepted or if labels are counted upon receipt.

o Designation of one individual to be responsible for storage and issuance of all labels.

o Receipt by the packaging and labeling department of a batch record, or other record, showing the quantity of labels needed for a batch. Determine if the batch record is retained by the packaging superviso or accompanies the labels to the actual packaging and labeling line.

o Adequate controls of the quantities of labeling issued, used, and returned. Determine if excess labels are accounted for and if excess labels bearing specific control codes, and obsolete or changed labels are destroyed.

o Inspection of the facilities before labeling to ensure that all previously used labeling and drugs have been removed.

o Assurance that batch identification is maintained during packaging.

o Control procedures to follow if a significant unexplained discrepancy occurs between quantity of drug packaged and the quantity of labeling issued.

o Segregated facilities for labeling one batch of the drug at a time. If this is not practiced, determine what steps are taken to prevent mix-ups.

o Methods for checking similar type labels of different drugs or potencies to prevent mixing.

o Quarantine of finished packaged products to permit adequate examination or testing of a representative sample to safeguard against errors. Also, to prevent distribution of any batch until all specified tests have been met.

o An individual who makes the final decision that the drug should go to the warehouse, or the shipping department.

o Utilization of any outside firms, such as contract packers, and what controls are exercised over such operations.

Special attention should be devoted to firms using "rolls" of pressure sensitive labels. Investigators have found instances where:

o Paper chips cut from label backing to help running the labels through a coder interfered with the code printer causing digits in the lot number to be blocked out.

o Some rolls contained spliced sections resulting in label changes in the roll.

o Some labels shifted on the roll when the labels were printed resulting in omitting required information.

The use of cut labels can cause a significant problem and should be evaluated in detail. Most firms are replacing their cut labels with roll labels.

Review prescription drugs for which full disclosure information may be lacking. If such products are found, submit labels and other labeling as exhibits with the EIR See 21 CFR 201.56 for the recommended sequence in which full disclosure information should be presented.

Review labels of OTC products for warnings required by 21 CFR 369.

A control code must be used to identify the finished product with a lot, or control number that permits determination of the complete history of the manufacture and control of the batch.

Determine:

o The complete key (breakdown) to the code.

o Whether the batch number is the same as the control number on the finished package. If not, determine how the finished package control number relates, and how it is used to find the identity of the original batch.

Beginning August 3, 1994 the following new requirements will become effective:

o Use of gang-printed labels will be prohibited unless they are adequately differentiated by size, shape or color. (211.122(f))

o If cut labels are used one of the following special control procedures shall be used (211.122(g)):

(1) Dedication of packaging lines.

(2) Use of electronic or electromechanical equipment to conduct a 100-percent examination of finished product.

(3) Use of visual inspection to examine 100-percent of the finished product for hand applied labeling. The visual examination will be conducted by one person and independently verified by a second person.

o Labeling reconciliation required by 211.125 is waived for cut or roll labeling if a 100-percent examination is performed according to 211.22(g)(2).

Holding and Distribution [21 CFR subpart H]

Check the finished product storage and shipping areas for sanitary condition, stock rotation, and special storage conditions needed for specific drugs. Evaluate any drugs that have been rejected, or are on hold for other than routine reasons.

Laboratory Controls [21 CFR Subpart I]

Laboratory controls should include adequate specifications and test procedures to assure that components in-process and finished products conform to appropriate standards of identity, strength, quality, and purity

In order to permit proper evaluation of the firm's laboratory controls, determine:

o Whether the firm has established a master file of specifications for all raw materials used in drug manufacture. This master file should include sampling procedures, sample size, number of containers to be sampled, manner in which samples will be identified, tests to be performed, and retest dates for components subject to deterioration.

o The firm's policies about protocols of assay. These reports are often furnished by raw material suppliers; however, the manufacturer is responsible for verifying the validity of the protocols by periodically performin their own complete testing and routinely conducting identity tests on all raw materials received.

o Laboratory procedure for releasing raw materials, finished bulk drugs or packaged drugs from quarantine. Determine who is responsible for this decision. Raw material specifications should include approved suppliers For NDA or ANDA drugs, the approved suppliers listed in their specifications should be the same as those approved in the NDA or ANDA.

o If the laboratory is staffed and equipped to do all raw material, in-process, and finished product testing that is claimed.

o Whether drug preparations are tested during processing. If so, determine what type of tests are made and whether a representative sample is obtained from various stages of processing.

o Specifications and description of laboratory testing procedures for finished products.

o Procedures for checking the identity and strength of all active ingredients including pyrogen and sterility testing, if applicable.

o If the laboratory conducts pyrogen tests, safety tests, or bioassays; determine the number of laboratory animals and if they are adequately fed and housed. Determine what care is provided on weekends and holidays.

o Sterility testing procedures.

Entries should be permanently recorded and show all results, both positive and negative. Examine representative samples being tested and their records. When checking the sterility testing procedures, determine:

1. Physical conditions of testing room. The facility used to conduct sterility testing should be similar to those used for manufacturing products.

2. Laboratory procedures for handling sterile sample.

3. Use of ultra-violet lights.

4. Number of units tested per batch.

5. Procedure for identifying test media with specific batches.

6. Test media's ability to support growth of organisms.

7. Length of incubation period.

8. Procedure for diluting products to offset the effects of bacteriostatic agents.

o Pyrogen testing procedures

Determine if animals involved in positive pyrogen tests are withdrawn from use for the required period.

If the L.A.L. Test is used, review the FDA "Guideline on Validation of the Limulus Amebocyte Lysate Test ***."

o If any tests are made by outside laboratories, report the names of the laboratories and the tests they perform. Determine what precautions the firm takes to insure that the laboratories' work is bona fide.

o Methods used to check the reliability, accuracy, and precision of laboratory test procedures and instrumentation.

o How final acceptance or rejection of raw materials, intermediates, and finished products is determined. Review recent rejections and disposition of affected items.

o The provisions for complete records of all data concerning laboratory tests performed, including dates and endorsements of individuals performing the tests, and traceability.

o For components and finished product, the reserve sample program and procedures should be evaluated. Challenge the system and determine if the samples are maintained and can be retrieved. The storage container must maintain the integrity of the product.

o Whether stability tests are performed on:

1. The drug product in the container and closure system in which marketed.

2. Solutions prepared as directed in the labeling at the time of dispensing. Determine if expiration dates, based on appropriate stability studies, are placed on labels.

o If penicillin and non-penicillin products are manufactured on the same premises, whether non-penicillin products are tested for penicillin contamination.

Obtain copies of laboratory records, batch records, and any other documents that show errors or other deficiencies.

Control Records [21 CFR Subpart J]

1. Master Production and Control Records [21 CFR 211.186]

The various master production and control records are important because all phases of production and control are governed by them. Master records, if erroneous, may adversely affect the product. These records must be prepared according to the drug CGMPR's outlined in 21 CFR 211.186. These records might not be in one location, but should be readily available for review.

2. Batch Production and Control Records [21 CFR 211.188]

The batch production and control records must document each significant step in the manufacture, labeling, packaging, and control of specific batches of drugs. 21 CFR 211.188 provides the basic information the batch records must provide. A complete production and control record may consist of several separate records which should be readily available to the investigator.

Routinely check the batch record calculations against the master formula record. Give special attention to those products on which there have been complaints.

Be alert for transcription errors from the master formula record to the batch record. Be alert for transcription or photocopying errors involving misinterpretation of symbols, abbreviations, and decimal points, etc.

It is important that batch production records be specific in terms of equipment (v-blender vs. ribbon blender) and processing times (mixing time and speed). The equipment should have its own unique identification number. The manufacturing process for these products must be standardized, controlled, and validated.

3. Distribution [21 CFR 211.196]

Complete distribution records should be maintained per 21 CFR 211.196. Be alert for suspicious shipments of products subject to abuse or which have been targeted for high priority investigation by the agency. These include steroids, counterfeits, diverted drugs (i.e.; physician samples, clinical packs, etc.).

Determine and evaluate if the firm checks on the authenticity of orders received. What references are used, e.g. current editions of the AMA Directory, Hays Directory, etc.

4. Complaint Files [21 CFR 211.198]

21 CFR 211.198 requires that records of all written and oral complaints be maintained. Although FDA has no authority to require a drug firm, except for prescription drugs, to open its complaint files, attempt to review the firm's files.

The complaint files should be readily available for review. Do a follow-up investigation on all applicable consumer complaints in the firm's district factory jacket. Review and evaluate the firm's procedures for handling complaints. Determine if all complaints are handled as complaints and not inappropriately excluded.

Review the complaints and determine if they were fully investigated. Evaluate the firm's conclusions of the investigation, and determine if appropriate corrective action was taken. Determine if the product should be recalled, or warrant a comprehensive investigation by FDA

Returned Drug Products [21 CFR Subpart K]

Returned drugs often serve as an indication that products may have decomposed during storage, are being recalled or discontinued.

Determine how returned drug items are handled. For example, are they quarantined, destroyed after credit, or returned to storage?

If an abnormally large amount of a specific drug item is on hand, determine why. Check if returned drug items are examined in the laboratory, and who makes the ultimate decision as to the use of the returned drugs.

Note: Dumping salvage drugs in the trash is a potentially dangerous practice. Advise management to properly dispose of the drugs to preclude salvage. Drugs should be disposed of in accordance with E.P.A. regulations.

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