

GUIDE TO INSPECTIONS ORAL SOLUTIONS AND SUSPENSIONS

Note: This document is reference material for investigators and other FDA personnel. The document does not bind FDA, and does not confer any rights, privileges, benefits, or immunities for or on any person(s).

I. INTRODUCTION

The manufacture and control of oral solutions and oral suspensions has presented some problems to the industry. While bioequivalency concerns are minimal (except for the antiseptic products such as phenytoin suspension), there are other issues which have led to recalls. These include microbiological, potency and stability problems. Additionally, because the population using these oral dosage forms includes newborns, pediatrics and geriatrics who may not be able to take oral solid dosage forms and may be compromised, defective dosage forms can pose a greater risk because of the population being dosed. Thus, this guide will review some of the significant potential problem areas and provide direction to the investigator when giving inspectional coverage.

II. FACILITIES

The design of the facilities are largely dependent upon the type of products manufactured and the potential for cross-contamination and microbiological contamination. For example, the facilities used for the manufacture of OTC oral products might not require the isolation that a steroid or sulfa product would require.

Review the products manufactured and the procedures used by the firm for the isolation of processes to minimize contamination. Observe the addition of drug substance and powdered excipients to manufacturing vessels to determine if operations generate dust. Observe the systems and the efficiency of the dust removal system.

The firm's HVAC (Heating Ventilation and Air Conditioning) system may also warrant coverage particularly where potent or highly sensitizing drugs are processed. Some manufacturers recirculate air without adequate filtration. Where air is recirculated, review the firm's data which demonstrates the efficiency of air filtration such should include surface and/or air sampling.

III. EQUIPMENT

Equipment should be of sanitary design. This includes sanitary pumps, valves, flow meters and other equipment which can be easily sanitized. Ball valves, packing in pumps and pockets in flow meters have been identified as sources of contamination.

In order to facilitate cleaning and sanitization, manufacturing and filling lines should be identified and detailed in drawings and SOPs. In some cases, long delivery lines between manufacturing areas and filling areas have been a source of contamination. Also, SOPs, particularly with regard to time limitations between batches and for cleaning have been found deficient in many manufacturers. Review cleaning SOPs, including drawings and validation data with regard to cleaning and sanitization.

Equipment used for batching and mixing of oral solutions and suspensions is relatively basic. Generally, these products are formulated on a weight basis with the batching tank on load cells so that a final Q.S. can be made by weight. Volumetric means, such as using a dip stick or line on a tank,

have been found to be inaccurate.

In most cases, manufacturers will assay samples of the bulk solution or suspension prior to filling. A much greater variability has been found with batches that have been manufactured volumetrically rather than by weight. For example, one manufacturer had to adjust approximately 8% of the batches manufactured after the final Q.S. because of failure to comply with potency specifications. Unfortunately, the manufacturer relied solely on the bulk assay. After readjustment of the potency based on the assay, batches occasionally were found out of specification because of analytical errors.

The design of the batching tank with regard to the location of the bottom discharge valve has also presented problems. Ideally, the bottom discharge valve is flush with the bottom of the tank. In some cases valves, including undesirable ball valves, have been found to be several inches to a foot below the bottom of the tank. In others, drug or preservative was not completely dissolved and was lying in the "dead leg" below the tank with initial samples being found to be subpotent. For the manufacture of suspensions, valves should be flush. Review and observe the batching equipment and transfer lines.

With regard to transfer lines, they are generally hard piped and easily cleaned and sanitized. In some cases manufacturers have used flexible hoses to transfer product. It is not unusual to see flexible hoses lying on the floor, thus significantly increasing the potential for contamination. Such contamination can occur by operators picking up or handling hoses, and possibly even placing them in transfer or batching tanks after they had been lying on the floor. It is also a good practice to store hoses in a way that allows them to drain rather than be coiled which may allow moisture to collect and be a potential source of microbial contamination. Observe manufacturing areas and operator practices, particularly when flexible hose connection are employed.

Another common problem occurs when a manifold or common connections are used, especially in water supply, premix or raw material supply tanks. Such common connections have been shown to be a source of contamination.

IV. RAW MATERIALS

The physical characteristics, particularly the particle size of the drug substance, are very important for suspensions. As with topical products in which the drug is suspended, particles are usually very fine to micronized (less than 25 microns). For syrups, elixir or solution dosage forms in which there is nothing suspended, particle size and physical characteristics of raw materials are not that important. However, they can affect the rate of dissolution of such raw materials in the manufacturing process. Raw materials of a finer particle size may dissolve faster than those of a larger particle size when the product is compounded.

Examples of a few of the oral suspensions in which a specific and well defined particle size specification for the drug substance is important include phenytoin suspension, carbamazepine suspension, trimethoprim and sulfamethoxazole suspension, and hydrocortisone suspension. Review the physical specifications for any drug substance which is suspended in the dosage form.

V. COMPOUNDING

In addition to a determination of the final volume (Q.S.) as previously discussed, there are microbiological concerns. For oral suspensions, there is the additional concern with uniformity, particularly because of the potential for segregation during manufacture and storage of the bulk suspension, during transfer to the filling line and during filling. Review the firm's data that support storage times and transfer operations. There should be established procedures and time limits for such operations to address the potential for segregation or settling as well as other unexpected effects that may be caused by extended holding or stirring.

For oral solutions and suspensions, the amount and control of temperature is important from a microbiological as well as a potency aspect. For those products in which temperature is identified as a critical part of the operation, the firm's documentation of temperature, such as by control charts, should be reviewed.

There are some manufacturers that rely on heat during compounding to control the microbiological levels in product. For such products, the addition of purified water to final Q.S., the batch, and the temperatures during processing should be reviewed.

In addition to drug substances, some additives, such as the parabens are difficult to dissolve and require heat. The control and assurance of their dissolution during the compounding stage should be reviewed. From a potency aspect, the storage of product at high temperatures may increase the level of degradants. Storage limitations (time and temperature) should be justified by the firm and evaluated during your inspection.

There are also some oral liquids which are sensitive to oxygen and have been known to undergo degradation. This is particularly true of the phenothiazine class of drugs, such as perphenazine and chlorpromazine. The manufacture of such products might require the removal of oxygen such as by nitrogen purging. Additionally, such products might also require storage in sealed tanks, rather than those with loose lids. Manufacturing directions for these products should be reviewed.

VI. MICROBIOLOGICAL

QUALITY

There are some oral liquids in which microbiological contamination can present significant health hazards. For example, some oral liquids, such as nystatin suspension are used in infants and immuno-compromised patients, and microbiological contamination with organisms, such as Gram-negative organisms, is objectionable. There are other oral liquid preparations such as antacids in which *Pseudomonas* sp. contamination is also objectionable. For other oral liquids such as cough preparations, the contamination with *Pseudomonas* sp. might not present the same health hazard. Obviously, the contamination of any preparation with Gram-negative organisms is not desirable.

In addition to the specific contaminant being objectionable, such contamination would be indicative of a deficient process as well as an inadequate preservative system. The presence of a specific *Pseudomonas* sp. may also indicate that other plant or raw material contaminants could survive the process. For example, the fact that a *Pseudomonas putida* contaminant is present could also indicate that *Pseudomonas aeruginosa*, a similar source organism, could also be present.

Both the topical and microbiological inspection guides discuss the methods and limitations of microbiological testing. Similar microbiological testing concepts discussed apply to the testing of oral liquids for microbiological contamination. Review the microbiological testing of raw materials, including purified water, as well as the microbiological testing of finished products. Since FDA laboratories typically utilize more sensitive test methods than industry, consider sampling any oral liquids in which manufacturers have found microbiological counts, no matter how low. Submit samples for testing for objectionable microorganisms.

VII. ORAL SUSPENSIONS

UNIFORMITY

Those liquid products in which the drug is suspended (and not in solution) present manufacturer and

control problems.

Those liquid products in which the drug is suspended (and not in solution) present manufacture and control problems. Depending upon the viscosity, many suspensions require continuous or periodic agitation during the filling process. If delivery lines are used between the bulk storage tank and the filling equipment, some segregation may occur, particularly if the product is not viscous. Review the firm's procedures for filling and diagrams for line set-up prior to the filling equipment.

Good manufacturing practice would warrant testing bottles from the beginning, middle and end to assure that segregation has not occurred. Such samples should not be composited.

In-process testing for suspensions might also include an assay of a sample from the bulk tank. More important, however, may be testing for viscosity.

VIII. PRODUCT

SPECIFICATIONS

Important specifications for the manufacture of all solutions include assay and microbial limits. Additional important specifications for suspensions include particle size of the suspended drug, viscosity, pH, and in some cases dissolution. Viscosity can be important from a processing aspect to minimize segregation. Additionally, viscosity has also been shown to be associated with bioequivalency. pH may also have some meaning regarding effectiveness of preservative systems and may even have an effect on the amount of drug in solution. With regard to dissolution, there are at least three products which have dissolution specifications. These products include phenytoin suspension, carbamazepine suspension, and sulfamethoxazole and trimethoprim suspension. Particle size is also important and at this point it would seem that any suspension should have some type of particle size specification. As with other dosage forms, the underlying data to support specifications should be reviewed.

IX. PROCESS VALIDATION

As with other products, the amount of data needed to support the manufacturing process will vary from product to product. Development (data) should have identified critical phases of the operation, including the predetermined specifications, that should be monitored during process validation.

For example, for solutions the key aspects that should be addressed during validation include assurance that the drug substance and preservatives are dissolved. Parameters, such as heat and time should be measured. Also, in-process assay of the bulk solution during and/or after compounding according to predetermined limits are also an important aspects of process validation. For solutions that are sensitive to oxygen and/or light, dissolved oxygen levels would also be an important test. Again, the development data and the protocol should provide limits. Review firm's development data and/or documentation for their justification of the process.

As discussed, the manufacture of suspensions presents additional problems, particularly in the area of uniformity. Again, development data should have addressed the key compounding and filling steps that assure uniformity. The protocol should provide for the key in-process and finished product tests, along with their specifications. For oral solutions, bioequivalency studies may not always be needed. However, oral suspensions, with the possible exception of some of the antacids, OTC products, usually require a bioequivalency or clinical study to demonstrate effectiveness. As with oral solid dosage forms, comparison to the biobatch is an important part of validation of the process.

Review the firm's protocol and process validation report and, if appropriate, compare data for full

scale batches to biobatch, data and manufacturing processes.

X. STABILITY

One area that has presented a number of problems includes the assurance of stability of oral liquid products throughout their expiry period. For example, there have been a number of recalls of the vitamins with fluoride oral liquid products because of vitamin degradation. Drugs in the phenothiazine class, such as perphenazine, chlorpromazine and promethazine have also shown evidence of instability. Good practice for this class of drug products would include quantitation of both the active and primary degradant. Dosage form manufacturers should know and have specifications for the primary degradant. Review the firm's data and validation data for methods used to quantitate both the active drug and degradant.

Because interactions of products with closure systems are possible, liquids and suspensions undergoing stability studies should be stored on their side or inverted in order to determine whether contact of the drug product with the closure system affects product integrity.

Moisture loss which can cause the remaining contents to become superpotent and microbiological contamination are other problems associated with inadequate closure systems.

XI. PACKAGING

Problems in the packaging of oral liquids have included potency (fill) of unit dose products, accurate calibration of measuring devices such as droppers that are often provided. The USP does not provide for dose uniformity testing for oral solutions. Thus, for unit dose solution products, they should deliver the label claim within the limits described in the USP. Review the firm's data to assure uniformity of fill and test procedures to assure that unit dose samples are being tested.

Another problem in the packaging of Oral Liquids is the lack of cleanliness of containers prior to filling. Fibers and even insects have been identified as debris in containers, and particularly plastic containers used for these products. Many manufacturers receive containers shrink-wrapped in plastic to minimize contamination from fiberboard cartons. Many manufacturers utilize compressed air to clean containers. Vapors, such as oil vapors, from the compressed air have occasionally been found to present problems. Review the firm's systems for the cleaning of containers.