GUIDE TO INSPECTIONS OF TOPICAL DRUG PRODUCTS

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I. PURPOSE

The purpose of this guide is to provide field investigators, who are familiar with the provisions of the Current Good Manufacturing Practice (CGMP) regulations for pharmaceuticals, with guidance on inspecting selected facets of topical drug product production. The subjects covered in the guide are generally applicable to all forms of topical drug products, including those that are intended to be sterile. However, this guide does not address every problem area that the investigator may encounter, nor every policy that pertains to topical drug products.

II. INTRODUCTION

This inspectional guide addresses several problem areas that may be encountered in the production of topical drug products potency, active ingredient uniformity, physical characteristics, microbial purity and chemical purity. The guide also addresses problems relating to the growing number of transdermal products. If a new drug pre-approval inspection is being conducted, then an examination of the filed manufacturing and control data, and correspondence should be accomplished early in the inspection. As with other pre-approval inspections, the manufacturing and controls information filed in the relevant application should be compared with the data used for clinical batches and for production (validation) batches. Filed production control data should be specific and complete.

III. POTENCY UNIFORMITY

Active ingredient solubility and particle size are generally important ingredient characteristics that need to be controlled to assure potency uniformity in many topical drug products such as emulsions, creams and ointments. Crystalline form is also important where the active ingredient is dispersed as a solid phase in either the oil or water phase of an emulsion, cream, or ointment.

It is important that active ingredient solubility in the carrier vehicle be known and quantified at the manufacturing step in which the ingredient is added to the liquid phase. The inspection should determine if the manufacturer has data on such solubility and how that data was considered by the firm in validating the process.

Substances which are very soluble, as is frequently the case with ointments, would be expected to present less of a problem than if the drug substance were to be suspended, as is the case with creams. If the drug substance is soluble, then potency uniformity would be based largely upon adequate distribution of the component throughout the mix.

If the active ingredient is insoluble in the vehicle, then in addition to assuring uniformity of distribution in the mix, potency uniformity depends upon control of particle size, and use of a validated mixing process. Particle size can also affect the activity of the drug substance because the smaller the particle size the greater its surface area, which may influence its activity. Particle size also affects the degree to which the product may be physically irritating when applied; generally, smaller particles are less irritating.

Production controls should be implemented that account for the solubility characteristics of the drug substance; inadequate controls can adversely affect product potency, efficacy and safety. For example, in one instance, residual water remaining in the manufacturing vessel, used to produce an ophthalmic ointment, resulted in partial solubilization and subsequent recrystallization of the drug substance; the substance recrystallized in a larger particle size than expected and thereby raised questions about the product efficacy.

In addition to ingredient solubility/particle size, the inspection should include a review of other physical characteristics and specifications for both ingredients and finished products.

IV. EQUIPMENT AND PRODUCTION CONTROL

Mixers

There are many different kinds of mixers used in the manufacture of topical products. It is important that the design of a given mixer is appropriate for the type of topical product being mixed. One important aspect of mixer design is how well the internal walls of the mixer are scraped during the mixing process. This can present some problems with stainless steel mixers because scraper blades should be flexible enough to remove interior material, yet not rigid enough to damage the mixer itself. Generally, good design of a stainless steel mixer includes blades which are made of some hard plastic, such as teflon, which facilitates scrapping of the mixer walls without damaging the mixer.

If the internal walls of the mixer are not adequately scraped during mixing, and the residual material becomes part of the batch, the result may be non-uniformity. Such non-uniformity may occur, for example, if operators use hand held spatulas to scrape the walls of the mixer.

Another mixer design concern is the presence of "dead spots" where quantities of the formula are stationary and not subject to mixing. Where such "dead spots" exist, there should be adequate procedures for recirculation or non-use of the cream or ointment removed from the dead spots in the tank.

Ideally, during the inspection, mixers should be observed under operating conditions.

Filling and Packaging

Suspension products often require constant mixing of the bulk suspension during filling to maintain uniformity. When inspecting a suspension manufacturing process determine how the firm assures that the product remains homogeneous during the filling process and audit the data that supports the adequacy of the firm's process. When the batch size is large and the bulk suspension is in large tanks, determine how the firm deals with low levels of bulk suspension near the end of the filling process. Does the bulk suspension drop below a level where it can be adequately mixed? Is residual material transferred to a smaller tank? Does the firm rely upon hand mixing of the residual material? The firm should have demonstrated the adequacy of the process for dealing with residual material.

Process Temperature Control

Typically, heat is applied in the manufacture of topicals to facilitate mixing and/or filling operations. Heat may also be generated by the action of high energy mixers. It is important to control the temperature within specified parameters, not only to facilitate those operations, but also to assure that product stability is not adversely affected. Excessive temperatures may cause physical and/or chemical degradation of the drug product, vehicle, the active ingredient(s), and/or preservatives. Furthermore, excessive temperatures may cause insoluble ingredients to dissolve, reprecipitate, or change particle size or crystalline form.

Temperature control is also important where microbial quality of the product is a concern. The processing of topicals at higher temperatures can destroy some of the objectionable microorganisms that may be present. However, elevated temperatures may also promote incubation of microorganisms.

Temperature uniformity within a mixer should be controlled. In addressing temperature uniformity, firms should consider the complex interaction among vat size, mixer speed, blade design, viscosity of the contents and the rate of heat transfer. Where temperature control is critical, use of recording thermometers to continuously monitor/document temperature measurements is preferred to frequent manual checks. Where temperature control is not critical, it may be adequate to manually monitor/document temperatures periodically by use of hand held thermometers.

V. CLEANING VALIDATION

It is CGMP for a manufacturer to establish and follow written SOPs to clean production equipment in a manner that precludes contamination of current and future batches. This is especially critical where contamination may present direct safety concerns, as with a potent drug, such as a steroid (e.g., cortisone, and estrogen), antibiotic, or a sulfa drug where there are hypersensitivity concerns.

The insolubility of some excipients and active substances used in the manufacture of topicals makes some equipment, such as mixing vessels, pipes and plastic hoses, difficult to clean. Often, piping and transfer lines are inaccessible to direct physical cleaning. Some firms address this problem by dedicating lines and hoses to specific products or product classes.

It is therefore important that the following considerations be adequately addressed in a firm's cleaning validation protocol and in the procedures that are established for production batches.

Detailed Cleaning Procedures

Cleaning procedures should be detailed and provide specific understandable instructions. The procedure should identify equipment, cleaning method(s), solvents/detergents approved for use, inspection/release mechanisms, and documentation. For some of the more complex systems, such as clean-in-place (CIP) systems, it is usually necessary to provide a level of detail that includes drawings, and provision to label valves. The time that may elapse from completion of a manufacturing operation to initiation of equipment cleaning should also be stated where excessive delay may affect the adequacy of the established cleaning procedure. For example, residual product may dry and become more difficult to clean.

Sampling Plan For Contaminants

As part of the validation of the cleaning method, the cleaned surface is sampled for the presence of residues. Sampling should be by an appropriate method, selected based on factors such as equipment and solubility of residues. For example, representative swabbing of surfaces is often used, especially in hard to clean areas and/or where the residue is relatively insoluble. Analysis of rinse solutions for residues has also been shown to be of value where the residue is soluble and/or difficult to access for direct swabbing. Both methods are useful when there is a direct measurement of the residual substance. However, it is unacceptable to test rinse solutions (such as purified water) for conformance to the purity specifications for those solutions, instead of testing directly for the presence of possible residues.

Equipment Residue Limits

Because of improved technology, analytical methods are becoming much more sensitive and capable of determining very low levels of residues. Thus, it is important that a firm establish appropriate limits on levels of post-equipment cleaning residues. Such limits must be safe, practical, achievable, verifiable and must ensure that residues remaining in the equipment will not cause the quality of subsequent batches to be altered beyond established product specifications. During inspections, the rationale for residue limits should be reviewed.

Because surface residues will not be uniform, it should be recognized that a detected residue level may not represent the maximum amount that may be present. This is particularly true when surface sampling by swabs is performed on equipment.

VI. MICROBIOLOGICAL

CONTROLS (NON-STERILE

TOPICALS)

The extent of microbiological controls needed for a given topical product will depend upon the nature of the product, the use of the product, and the potential hazard to users posed by microbial contamination. This concept is reflected in the Current Good Manufacturing (CGMP) regulations at 21 Code of Federal Regulations (CFR) 211.113(a) (Control of microbiological contamination), and in the U.S. Pharmacopeia (USP). It is therefore vital that manufacturers assess the health hazard of all organisms isolated from the product.

Deionized Water Systems For Purified Water

Inspectional coverage should extend to microbiological control of deionized water systems used to produce purified water. Deionizers are usually excellent breeding areas for microorganisms. The microbial population tends to increase as the length of time between deionizer service periods increases. Other factors which influence microbial growth include flow rates, temperature, surface area of resin beds and, of course, the microbial quality of the feed water. These factors should be considered in assessing the suitability of deionizing systems where microbial integrity of the product incorporating the purified water is significant. From this assessment, a firm should be able to design a suitable routine water monitoring program and a program of other controls as necessary.

It would be inappropriate for a firm to assess and monitor the suitability of a deionizer by relying solely upon representations of the deionizer manufacturer. Specifically, product quality could be compromised if a firm had a deionizer serviced at intervals based not on validation studies, but rather on the "recharge" indicator built into the unit. Unfortunately, such indicators are not triggered by microbial population, but rather they are typically triggered by measures of electrical conductivity or resistance. If a unit is infrequently used, sufficient time could elapse between recharging/sanitizing to allow the microbial population to increase significantly.

Pre-use validation of deionizing systems used to produce purified water should include consideration of such factors as microbial quality of feed water (and residual chlorine levels of feed water where applicable), surface area of ion-exchange resin beds, temperature range of water during processing, operational range of flow rates, recirculation systems to minimize intermittent use and low flow, frequency of use, quality of regenerant chemicals, and frequency and method of sanitization.

A monitoring program used to control deionizing systems should include established water quality and conductivity monitoring intervals, measurement of conditions and quality at significant stages through the deionizer (influent, post cation, post anion, post mixed-bed, etc.), microbial conditions of the bed, and specific methods of microbial testing. Frequency of monitoring should be based upon the firm's

experience with the systems.

Other methods of controlling deionizing systems include establishment of water quality specifications and corresponding action levels, remedial action when microbial levels are exceeded, documentation of regeneration and a description of sanitization/ sterilization procedures for piping, filters, etc..

Microbiological Specifications and Test Methods

During inspections it is important to audit the microbiological specifications and microbial test methods used for each topical product to assure that they are consistent with any described in the relevant application, or U.S.P.. It is often helpful for the inspection to include an FDA microbiologist.

Generally, product specifications should cover the total number of organisms permitted, as well as specific organisms that must not be present. These specifications must be based on use of specified sampling and analytical procedures. Where appropriate, the specifications should describe action levels where additional sampling and/or speciation of organisms is necessary.

Manufacturers must demonstrate that the test methods and specifications are appropriate for their intended purpose. Where possible, firms should utilize methods that isolate and identify organisms that may present a hazard to the user under the intended use. It should be noted that the USP does not state methods that are specific for water insoluble topical products.

One test deficiency to be aware of during inspections is inadequate dispersement of a cream or ointment on microbial test plates. Firms may claim to follow USP procedures, yet in actual practice may not disperse product over the test plate, resulting in inhibited growth due to concentrated preservative in the non- dispersed inoculate. The spread technique is critical and the firm should have documentation that the personnel performing the technique have been adequately trained and are capable of performing the task. Validation of the spread plate technique is particularly important where the product has a potential antimicrobial affect.

In assessing the significance of microbial contamination of a topical product, both the identification of the isolated organisms and the number of organisms found are significant. For example, the presence of a high number of organisms may indicate that the manufacturing process, component quality, and/or container integrity may be deficient. Although high numbers of non-pathogenic organisms may not pose a health hazard, they may affect product efficacy and/or physical/chemical stability. Inconsistent batch to batch microbial levels may indicate some process or control failure in the batch. The batch release evaluation should extend to both organism identification and numbers and, if limits are exceeded, there should be an investigation into the cause.

Preservative Activity

Manufacturing controls necessary to maintain the anti- microbiological effectiveness of preservatives should be evaluated by the firm. For example, For those products that separate on standing, the firm should have data that show the continued effectiveness of the preservative throughout the product's shelf-life.

For preservative-containing products, finished product testing must ensure that the specified level of preservative is present prior to release. In addition, preservative effectiveness must be monitored as part of the final on-going stability program. This can be accomplished through analysis for the level of preservative previously shown to be effective and/or through appropriate microbiological challenge at testing intervals.

For concepts relating to sterility assurance and bioburden controls on the manufacture of sterile

topicals see the Guideline On Sterile Drug Products Produced by Aseptic Processing.

VII. CHANGE CONTROL

As with other dosage forms, it is important for the firm to carefully control how changes are made in the production of topical products. Firms should be able to support changes which represent departures from approved and validated manufacturing processes.

Firms should have written change control procedures that have been reviewed and approved by the quality control unit. The procedures should provide for full description of the proposed change, the purpose of the change, and controls to assure that the change will not adversely alter product safety and efficacy. Factors to consider include potency and/or bioactivity, uniformity, particle size (if the active ingredient is suspended), viscosity, chemical and physical stability, and microbiological quality.

Of particular concern are the effects that formulation and process changes may have on the therapeutic activity and uniformity of the product. For example, changes in vehicle can affect absorption, and processing changes can alter the solubility and microbiological quality of the product.

VIII. TRANSDERMAL TOPICAL

PRODUCTS

Inspections of topical transdermal products (patches) have identified many problems in scale-up and validation. Problems analogous to production of topical creams or ointments include uniformity of the drug substance and particle size in the bulk gel or ointment. Uniformity and particle size are particularly significant where the drug substance is suspended or partially suspended in the vehicle. Viscosity also needs control because it can affect the absorption of the drug; the dissolution test is important in this regard.

Other areas that need special inspectional attention are assembly and packaging of the patch, including adhesion, package integrity (regarding pinholes) and controls to assure that a dose is present in each unit.

Because of the many quality parameters that must be considered in the manufacture and control of a transdermal dosage form, scale- up may be considerably more difficult than for many other dosage forms. Therefore, special attention should be given to evaluating the adequacy of the process validation efforts. As with other dosage forms, process validation must be based on multiple lots, typically at least three consecutive successful batches. Inspection of summary data should be augmented by comparison to selected data contained in supporting batch records, particularly where the data appear unusually uniform or disparate. Given the complexities associated with this dosage form, you may encounter tolerances and/or variances broader than for other dosage forms. In addition, batches may not be entirely problem-free. Nevertheless, the firm should have adequate rationale for the tolerances and production experiences, based on appropriate developmental efforts and investigation of problems.

IX. OTHER REFERENCES

Other relevant inspection guides that should be used in conjunction with this guide include:

o Guide to Inspections of Validation of Cleaning Processes.

o Guide to Inspections of High Purity Water Systems