NADA REVIEW OF DOSAGE FORM ORAL ELECTROLYTES

The Federal Food, Drug, and Cosmetic Act contains separate provisions for foods and drugs, and the agency has traditionally treated foods and drugs as separate classes of substances. However, there are products ordinarily thought of as "food" as defined in Section 201(f) of the Act which, based on stated or implied claims, may also fall within the definition of "drug" in Section 201(g). FDA ordinarily regulates such products as drugs.

Oral electrolytes are dosage form products intended for the mitigation of fluid and electrolyte losses and subsequent disruptions of metabolic activity. These products contain essential nutrients such as sugars, electrolytes and amino acids that ordinarily are regulated as foods. However, the products are drugs under section 201(g) because they are "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals." Further, oral electrolytes ordinarily are new animal drugs under section 201(w). Oral electrolyte products that are new animal drugs must be approved by FDA prior to marketing. Obtaining approval of a new animal drug application (NADA) for oral electrolytes has been difficult for sponsors. Such products typically contain a number of active ingredients, and it has not been feasible for sponsors to meet all aspects of CVM's Guideline for Drug Combinations for Use in Animals. That guideline calls for studies to show that each active ingredient in a combination drug makes a contribution to the effectiveness of the combination. CVM has determined that the purpose of its combination policy can be met by an alternative means in the case of oral electrolytes. That alternative means is explained below.

In addition, current CVM guidelines are not oriented toward evaluating the nutritional and dietary considerations that are central to a determination of the therapeutic usefulness of dosage form electrolyte products. Further, these products differ, in their nature and, often, their mechanism of action and toxicity, from most other new animal drugs that the Center reviews.

1. Purposes:

   This document discusses how the statutory requirement for a demonstration of effectiveness can be met in the case of an oral electrolyte. It also provides guidance for meeting the safety requirements and certain other requirements for approval.

2. **Application Procedures and Contents:**

Applications will be filed as NADAs under Section 512(b) of the Act. NADAs must be submitted in the form described in 21 CFR 514.1. Following is guidance for specific areas of the submission.

a. Evidence to Establish Effectiveness

The application must contain substantial evidence that the proposed oral electrolyte product has the effect it purports or is represented to have under the conditions prescribed, suggested, or recommended in the proposed labeling. Substantial evidence consists of reports of adequate and well-controlled studies, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the product.

The effectiveness of each essential nutrient component in the oral electrolyte product will be established by:

1) performance of controlled trials and/or,

2) published reports, authoritative texts, or treatises documenting established nutritional or medical principles.

Essential nutrients consist of those nutrients (proteins, minerals, carbohydrates, fats, vitamins) necessary for growth, normal function, and maintenance of life in the intended species and at the intended stage of life.

The Center wi11 review the submitted data and/or Iiterature and wi11 determine the effectiveness and appropriateness of each essential nutrient component, both individually and together, on the basis of generally accepted and documented nutritional and/or medical principles. Thereafter, the accepted essential nutrient components in the formulation will be evaluated as a single entity for purposes of demonstration of effectiveness, which as explained above will be by adequate and well-controlled studies.

Any configurational change in the chemical structure of an essential nutrient may require new proof of the effectiveness of that specific chemical entity in order to be incorporated into the formulation. Each active ingredient which is not accepted as an essential nutrient in the formulation must be shown to be effective, as mandated under 21 CFR 514.1(b)(8)(v), pertaining to combination products, and should follow the CVM Guidelines for Drug Combinations for Use in Animals.

b. Evidence to Establish Target Animal Safety

The safety for the product formulation must be demonstrated by adequate tests by all methods reasonably applicable as required by the Act and regulations. Inactive ingredients that have not previously been deemed to be safe by FDA need to be shown to be safe by accepted toxicologic testing procedures. Products should be clinically tested to ensure that when used as labeled they do not cause adverse effects from excessive levels of any single or multiple component(s).

c. Human Food Safety Requirements

Human food safety data need to be evaluated for both the essential nutrient component, and other ingredients (active and inactive) in accordance with Center guidelines if intended for use in food-producing animals.

d. Environmental Impact Requirements

The application must include an environmental assessment (EA) that contains the information presented in the format stated in 21 CFR 25.31a. If the product consists of substances that are demonstrated to be naturally occurring in the environment, an EA containing the information and presented in the format stated in 21 CFR 25.3la(b)(5) may be provided.

e. Manufacturing Methods, Facilities and Controls

1. GMP Compliance

Oral electrolytes are pharmaceutical dosage forms, and the manufacture of the finished dosage form is subject to the Current Good Manufacturing Practices under 21 CFR 211 and applicable guidelines.

However, the NADA requirements for the bulk active ingredients for oral electrolyte products may be met by an alternative means that would not necessarily require the filing of a Drug Master File (DMF) for bulk active components and the evaluation of the facilities as bulk pharmaceutical chemical manufacturers subject to the Good Manufacturing Practices under 21 CFR 211 and applicable guidelines.

The Center in regulating oral electrolytes as drug products recognizes that these products often contain essential nutrients that are normally regulated as foods and that the food grade components are of sufficient quality and purity to assure the safety of these components in oral products. For purposes of this guide, the policy in this limited instance is that USP grade/food grade components, although lacking a DMF, are acceptable for an NADA filing. Suitable testing and specifications must be established for all non-USP bulk components and complete testing of all batches of non-USP grade components should be performed prior to release for manufacture of the finished pharmaceutical dosage form.

2. Stability

Oral electrolyte solutions may be available as soluble powders, concentrated solutions or suspensions, or solutions ready for use. In all cases the product, at the time of use, should meet the general requirements for chemical stability and maintain, under expected storage conditions, a reasonable degree of physical integrity, such as absence of caking, sticking, gross discoloration, or irreversible loss of suspension or solution of the product. Moisture content and solubility (completeness of dissolution) of soluble powder products should be tested. In addition to testing for drug strength, products should also be tested for pH, osmolality, caloric density, and buffering capacity of the solution.

Products are expected to remain stable for the projected shelf life. Samples should be tested both at 25 and 37 to 40 degrees Celsius. Stability studies should provide assurance that the potency of any vitamins will not be less than 90 percent of that in the formulation during the designated shelf life and under the storage conditions specified in the labeling.

The stability of reconstituted products should also be determined after they are constituted according to the recommended labeling. Maintenance of adequate physical and chemical stability of partially used liquid products is necessary. If a reconstituted product shows, degradation, a label restriction against reuse may be requested.

f. Labeling

A quantitative declaration of the amounts of the essential nutrients and active ingredients should be provided on the labeling. These amounts should be declared in appropriate units as used according to label directions. Osmolality (mOsm/L), caloric density (kcal/L), and buffering capacity (mEq/L) "as used" should also be included. In addition, a list of all ingredients in descending order of predominance by weight should be provided.