Chapter VI

Human Studies:

This chapter presents general guidelines for the conduct of human clinical studies on foods and food ingredients. It also describes the types of human epidemiology data that may be useful to the Agency in assessing the safety of direct food additives and color additives used in food. Because human clinical studies were not included in the 1982 guidelines for direct food additives and color additives used in food, important issues related to these studies are discussed at length in this chapter.

The Agency does not require petitioners to conduct human clinical studies to support the safety of direct food additives and color additives used in food. However, petitioners may elect to perform such studies in certain circumstances, such as when the proposed additive will be consumed by humans at relatively high levels (see **Chapter VII B**). When petitioners conduct human clinical studies on substances intended for use as direct food additives and color additives used in food, however, the Agency recommends that the studies conform to the guidelines presented in this section. As usual, the Agency strongly recommends that petitioners planning to conduct human studies in support of the safety of direct food additives and color additives used in food consult with the Agency before the studies begin.

VI A. Clinical Evaluation of Foods and Food Additives

A major objective in the clinical testing of food and food additives is to assess aspects of safety that cannot be addressed adequately by non-human studies or by existing data on population exposure. For example, the Agency is now confronted with petitions for direct food additives that are intended to substitute for major nutrients such as fat and sugar. Because segments of our population may be exposed to large quantities of these additives for long periods of time, traditional methods of evaluating the safety of these substances may not be adequate. Testing these substances in animals at doses that greatly exaggerate their anticipated human exposures may not be possible. For these substances, human clinical studies may provided additional confidence in the safety of the food or food additive.

A food or food additive generally will be considered suitable for clinical testing if the substance is unlikely to produce significant toxic effects at the levels to which the subjects of the clinical study will be exposed. This usually is determined from the results of toxicity studies in animals or by examining existing data on population exposure. However, in cases where the type of toxic response associated with the consumption of a food or food additive by experimental animals is judged to be severe, exposure of subjects in clinical studies to the additive may need to be significantly below the level found to produce no toxic effects in an appropriate species.

Unlike patients participating in clinical trials of new drugs, no health benefit is anticipated for most test subjects in clinical studies of foods and food additives. Thus, the nature and weight of evidence required to establish the safety of these products for humans before clinical studies can begin may differ from that required to support testing under guidelines for investigational new drugs. Clinical studies of foods and food additives will focus on demonstrating safety; for example, the safety of an additive that may interfere with absorption of nutrients, whose status in the population is uncertain, may need to be evaluated in a clinical study.

1. General Considerations for Clinical Studies of Foods and Food Additives

Principles for the conduct of clinical trials are contained in the May 8, 1979 Federal Register: "*Statement concerning adequate and well-controlled clinical investigations.*" [1] The following guidelines identify general considerations for clinical studies of foods and food additives. Each consideration should be explicitly addressed in the clinical study's protocol.

- Before undertaking costly and time-consuming clinical studies as part of the safety assessment of a food or food additive, the investigator needs to formulate a defensible rationale for conducting human clinical studies and a clear set of objectives.

- Adequate preclinical investigations (including toxicity tests in animals) must have been completed. Results of these tests must establish that there is no expected toxicity to man at doses to be used in clinical studies. A clear, concise description of the design of pre-clinical studies and their results should be presented to FDA. Information about the history of use of the food or food additive outside the United States and documentation of the results of foreign clinical studies involving the food or food additive should also be presented for review.

- In designing protocols for clinical studies, the following should be considered: 1) the results of pre-clinical studies (including toxicity tests in animals) and foreign clinical studies; 2) the chemical nature of the proposed additive; and 3) all organs and organ systems that may be affected in man by consumption of the food or food additive under investigation.

- The sequence of clinical tests should be designed to maximize the safety of the research subjects.

- Guidelines for clinical trials of investigational new drugs should be followed in evaluating the qualifications of the principal investigator and investigating institution. In particular, careful consideration must be given to the qualifications of the investigator and the suitability of the investigating institution's facilities for conducting short- and long-term clinical trials.

FDA recognizes the need for the investigator to exercise sound clinical judgement based on his/her experience in an appropriate field of study. Studies involving healthy volunteers should be performed by investigators skilled in the evaluation of the safety of a variety of compounds. When subjects of a clinical study have a specific disease, as may be the case for clinical evaluation of foods for special dietary uses or special medical purposes, the investigators should be clinicians expert in the disease and disease process.

- The investigator should have high regard for the rights and safety of the test subject(s). The investigator is responsible for the administration of the food additive; thus, he/she must bear the ultimate responsibility for the welfare of the test subjects. All aspects of a clinical study generally are described in the study's protocol; however, because actions that have been identified as being in the best interests of the subjects at the beginning of a clinical study may change during the study, all aspects of the study must remain flexible and subject to modification. Aspects of the clinical study protocol subject to such modification include: 1) The nature and frequency of laboratory tests, 2) the duration of consumption of the food or food additive, and 3) the interval between test subjects' visits to the investigator.

Institutional review of research involving human subjects and the requirement for informed consent will provide additional safeguards for test subjects. Principles of institutional review and informed consent were set forth in the March 13, 1975 Federal Register: "*Technical Amendments Concerning Protection of Human Subjects*;"[2] these are summarized in **Appendix A** (see section VI A 5 below).

- There is some finite risk associated with the administration of every unapproved food and food additive to subjects of a clinical study; despite strict adherence to guidelines, the safety of subjects in the study cannot be guaranteed. Before beginning a clinical study, the investigator should consider what procedures will be used to detect adverse reactions to the test substance during the study. The

investigator should establish criteria that will be used to decide when to discontinue the clinical study; these criteria may be changed during the study if the change is required to support the safety of the subjects.

To further protect the safety of subjects of a clinical study, the sponsor of the study should provide appropriate follow-up after the study has ended. Such follow-up should be conducted or supervised by the investigator of the clinical study.

- Before a clinical study begins, the investigator should consider ways in which quality control of the study will be documented. Effective documentation of quality control will facilitate Agency review of the completed clinical study.

- FDA recommends that investigators use statistical expertise in the planning, design, execution, and analysis of pre-clinical and clinical studies. Such expertise will help ensure that the planned studies will provide the necessary information while minimizing the number of subjects (sample size estimation) and will strengthen the validity of estimates of safety obtained from the studies.

2. Specific Considerations for Clinical Studies of Foods and Food Additives

This section describes specific considerations concerning the protocol design, definition of study population, and statistical analysis of the results of human clinical studies with foods and food additives. These considerations should be explicitly addressed in the clinical study protocol.

a. Protocol Design

Protocols for clinical studies of foods and food additives should be described clearly and in sufficient detail to permit effective review and evaluation by CFSAN. In general, the protocol should be strictly adhered to throughout the clinical study; if the protocol is not adhered to, documentation of necessary modifications should be made (see item 7 in section 1 above). While it is rational and desirable to design studies to obtain specific information about the test substance, the generation of data justifying conclusions other than those originally anticipated can be a valuable result of clinical investigation.

The following are additional recommendations for the design of clinical study protocols for foods and food additives:

- A clear statement of objectives should be provided for each protocol. Good planning usually produces research questions that can be answered by direct inference from the study data. Since studies are frequently designed to answer more than one question, it is useful to list the questions to be answered in order of their priority.

- The rationale for conducting a clinical study should be presented. In addition, pre-clinical and clinical data relevant to the compound being studied and to the proposed protocol should be reviewed.

- A statement explaining the reasons for deciding on a particular length for the clinical study should be included in the protocol. In general, a clinical study should be of sufficient length to permit the demonstration of the safety (or lack of safety) of a food or food additive.

- A statement explaining the reasons for selecting particular dietary levels (dosages) of the food or food additive being tested should be included.

- Experimental design should include appropriate controls. When feasible, studies should be performed blind to avoid selection bias and bias in patient and physician responses.

- Investigators should describe proposed methods of randomization and should present analyses that demonstrate the effectiveness of these methods.

- Objective observation methods should be used when possible and appropriate, observational endpoints should be rigorously defined, and methodology that will be used to quantify endpoints should be described. A statement describing quality control and frequency of data collection (endpoint monitoring) also should be included.

- Limitations that may be imposed on the clinical study because of protocol design or the failure of subjects to comply with the written protocol (such as withdrawals from the study, failure to randomize subjects effectively, technological limits of observations, *etc.*) and the possible effects these limitations may have on the outcome of the study should be addressed.

b. The Study Population

Clinical studies identify physiological responses to test substances in well-defined, small populations. These results are used to make inferences about responses to the test substance in larger, target populations. Study protocols should specify how subjects will be selected, their assignment to alternative test regimens, the specific conditions under which the trial will be conducted, and the nature of the target population to which the subjects' responses will be extrapolated. The following are additional recommendations for defining and selecting subjects for the clinical study:

- Each study protocol must be reviewed and approved by the appropriate Institutional Review Board; written, informed consent must be obtained for each subject in the study (see **Appendix A** in section VI A 5 below).

- Protocols should clearly define the selection criteria for subjects, including diagnostic criteria and reasons for exclusion from the study, and should compare and contrast the study population with the larger population likely to consume the food or food additive.

- Criteria for discontinuing the study should be stated clearly.

- Doses of the test substance should be selected so that a range of subject responses to the substance can be observed and the highest safe dose of the proposed additive can be determined. When individual subjects' responses are expected to be quite variable, testing at multiple doses in a double-blind, placebo-controlled study is recommended.

- A serious problem in clinical studies is determining the degree of subject adherence to the assigned protocol. Careful attention to subject compliance with the protocol is particularly important in outpatient studies. Protocols should state clearly how subjects' compliance will be monitored and should indicate when noncompliance will result in discontinuing the subject in the study. In general, data on subject compliance and noncompliance enhance the credibility of a study.

If it becomes apparent during the study that subjects are not complying with the study protocol, reasons for their noncompliance should be determined. All subjects initially included in a study must be reported on in the study's results, regardless of the degree of their compliance. Some noncompliance may necessitate identifying subgroups for evaluation, such as subjects who fail to consume foods containing the additive and subjects who report excessive use of alcohol or medication.

- The number of subjects to be included in the study should be sufficient to be able to determine the safety of the test substance. Statistical estimates of the required number of subjects will depend upon: 1) The desired limit of detection of subjects' responses to the test substance; 2) the desired assurance against a false positive result; and 3) the acceptable risk of a false negative result.

- While it is desirable that placebo groups be included in early clinical studies of proposed foods and food additives (see page 17), this is not a requirement. Goals of early clinical studies may be 1) to gradually increase the dose of the test substance until physiological effects are observed or 2) to determine absorption and metabolism in humans in an effort to assess the adequacy of animal models used in safety assessments of the test compound. Therefore, subjects must be under careful observation during these studies.

The goals of early clinical studies often can be achieved effectively with an open (non-blind) study protocol. When clinical studies using blind comparisons of the test substance and a placebo or positive control substance should begin varies with the nature of the test material. During all phases of clinical investigation, the objective in using a placebo is to provide an adequate control for the compound under study. However, other methods of adequately controlling clinical studies exist. For example, the use of an active control compound or demonstration of a positive dose response to the food or food additive may constitute adequate control in some studies. For situations in which the natural course of a disease or condition is predictable and for which objective measurements of therapeutic or prophylactic response to the test compound can be made, results of carefully executed, open (non-blind) studies may be compared to historical data.

- Food additives should be studied in all age groups that may be significantly exposed, including, as appropriate, children, women of childbearing potential, older populations, and populations with specific disease conditions. The latter category includes populations that may be particularly exposed to, positively affected by, or at risk from a particular food or food additive.

Pregnancy tests should be administered to women of childbearing potential before the introduction of the test substance and the subject should be advised about suitable contraceptive measures. In general, women of childbearing potential should be excluded from the earliest clinical studies of a test substance. Once an adequate baseline of clinical information about the safety of a food or food additive has been obtained, however, women of childbearing potential may be included in clinical studies. For example, women of childbearing potential may participate in clinical studies when the teratogenic potential of the test substance has been determined to be negative in animals.

Follow-up to detect possible effects of the test substance on the fetus should be provided to women who become pregnant while on the study. Under these circumstances, transplacental passage of the substance and its secretion in milk should be assumed until proven otherwise.

- If the proposed food or food additive has a significant potential for use in children, its safety should be evaluated in children. Usually, studies in children are not attempted until there has been considerable clinical experience with the additive in adults. For certain proposed food additives, however, early clinical study in children may be warranted; in such cases, it is preferable to begin with older children, followed by younger children, infants, and premature infants. Detailed comments on pediatric studies are contained in "*General Considerations for the Clinical Evaluation of Drugs in Infants and Children*."[3] Additional examples of guidelines concerning the clinical testing of foods or food additives in children are provided by the American Academy of Pediatrics.[4,5]

- Generally, physical examinations and laboratory tests should be performed to screen individuals with medically significant abnormalities from the clinical study. Laboratory tests should include the following: 1) Electrocardiograph; 2) urinalysis; 3) various tests on blood samples (for example, complete blood counts including platelet estimates, blood urea nitrogen, serum creatinine, tests of liver function, fasting blood sugar or 2-hour postprandial blood sugar, electrolytes, protein, and albumin); and 4) other tests that may be indicated by the nature of the test compound or from the results of previous animal and human clinical studies (for example, tests of vitamin status, prothrombin time, and blood lipid profiles).

- In early clinical studies, when feasible, all subjects should refrain from taking medication (including over-the-counter drugs) for at least two (and preferably four) weeks before the study begins, unless interactions of the test substance with medication are the focus of the study. In some cases, a longer "washout" period will be required for return to a normal physiologic state before the clinical study begins.

In later clinical studies, it may be desirable to examine the safety of combinations of the test substance and medication(s).

◙ Post-study physical examinations for subjects of clinical studies often are necessary to ensure the subjects' safety. The results of these examinations should be fully documented.

c. Statistical Analyses

The following are general recommendations for statistical analyses in clinical studies of foods and food additives. Additional recommendations are contained in **Chapter IV B 4**.

◙ Investigators are encouraged to seek expert biostatistical assistance prior to formulating the study design.

◙ *A priori* description of the statistical methods to be used in analyzing data from a clinical study should be provided in the study's protocol.

◙ Estimates of statistical power should be used to help determine the optimal number of subjects for a clinical study.

3. Sequence of Clinical Studies for Foods and Food Additives

The rationale behind serially conducted studies is that results of each study may influence the plan of succeeding studies. Investigators are encouraged to discuss data from animal studies and early clinical studies with CFSAN before conducting additional clinical studies.

a. Early Clinical Studies

The purpose of these studies is to determine the metabolism and the level of the food or food additive that gives an adverse or toxic response in man. Physiologic processes that are of primary interest in early clinical studies include: 1) Disposition (absorption, biotransformation, and excretion) of the food or food additive and its metabolites; 2) the potential of the food or food additive to induce enzyme levels or increase activity; 3) interactions between the food or food additive and nutrients that may necessitate balance studies; and 4) interactions between the food or food additive and medications that may necessitate drug bioavailability or drug metabolism studies. Information about the potential use of the test substance and all preclinical information about the test substance should factor into decisions about the appropriate sequence of early clinical studies.

For both ethical and scientific reasons, the initial introduction of a food or food additive into humans should be done with carefully selected subjects. Subjects for early clinical studies should be "normal" volunteers. "Normal" generally means volunteers who are free from health problems that would complicate the interpretation of the study or increase the sensitivity of the subject to the toxic potential of the food or food additive. Children, pregnant women, and women of childbearing potential usually should be excluded from early clinical studies.

Within the limitations described in the preceding paragraph, subjects of early clinical studies should be selected to accurately reflect the general population. Thus, individuals with mild but stable illnesses such as uncomplicated hypertension or arthritis may be considered for inclusion in initial clinical studies on a food or food additive. It also may be permissible--and even desirable--to include subjects with abnormalities for which consumption of the food or food additive may be particularly beneficial. For example, subjects with hyperlipoproteinemia may be included in an early clinical study on a food or food additive that functions as a non-caloric fat substitute. Additional examples include: (a) A food or food additive that will be used in the dietary management of organ failure should be tested in a population with failure of the organ under study; (b) a food or food additive designed to be deficient in a particular nutrient should be tested in a population that is unable

to metabolize the nutrient in question (in fact, such a food or food additive may be harmful to a population with normal metabolism).

Most early clinical studies are sub-chronic (relatively short-term) and are generally less than 4 weeks in duration. These studies vary from single exposure to multiple exposures and examine a range of levels (doses) of the food or food additive. When several doses are being tested in a study, no research subject should be given the next-higher dose until sufficient exposure has occurred with the immediately preceding dose to be certain that serious adverse effects have not occurred.

For each food and food additive subjected to clinical investigation, it is also important to consider the appropriate frequency of laboratory tests and, when indicated by the results of previous studies, tests for specific organ or organ system effects. Independent of the outcome of clinical studies, thorough physical examinations and blood screening should be part of the follow-up for all subjects.

When unanticipated side effects occur in clinical studies, the investigator should determine the time required for elimination of the compound from the subject's system and reversal of the effects.

b. Further Clinical Studies

Additional clinical studies may be designed to determine the safety of the proposed food additive during chronic intake (relatively long-term) and to gather more information about the food additive's adverse effects in humans. These studies should be performed after the general safety of the food or food additive in humans has been established in early, short-term clinical studies. The duration of exposure to the food or food additive in these studies will vary with the nature of the additive. Chronic administration in humans usually means continuous consumption for at least 8 to 12 weeks, unless contraindicated by adverse side-effects.

Relatively long-term clinical studies of food and food additives may emphasize the physiologic processes of enzyme induction or interaction of the additive with other substances (such as nutrients, medications, and other food additives). In addition, when designing studies to determine the safety of chronically consumed food additives, investigators should consider conducting nutrient balance studies; these studies help determine end-organ (or end-organ system) responses to the additive, including neurobehavioral changes.

Finally, clinical studies may be performed to obtain information about adverse effects of the food or food additive on specific subpopulations. For these studies, appropriate subpopulations may include children, pregnant women, women of childbearing potential, and older subjects. These studies may also include subjects with concomitant diseases who are undergoing therapy for the disease, particularly if such subjects represent segments of the population who are likely to consume the food or food additive after it has been approved.

Relatively long-term clinical studies should include a limited number of closely monitored subjects (rarely exceeding several hundred). In the clinical studies described above, the frequency of physical examinations and laboratory tests for subjects will depend upon the nature and relative safety of the food additive. For some subjects, daily supervision may be necessary. Early periods during a study will typically involve more frequent supervision of subjects than later periods. An example of a graded supervision plan would be one in which a test subject is seen by the investigator at least once a week for 2 to 4 weeks, once every other week for 6 to 8 weeks, at monthly intervals for 2 to 3 months, and bimonthly until the end of the follow-up period. Routine laboratory tests should be performed at frequent intervals; frequency and type of special laboratory tests should be determined by the nature of the food or food additive and its intended use.

In both early and chronic clinical studies of food additives, it is particularly important that a single formulation of the test substances be used throughout the study; in addition, investigators should test the compounds that will be marketed. Consideration should be given to relative exposures for particular food uses when such uses may alter the structure or effects of the test substance. A significant change in the formulation or manufacture of the food or food additive during chronic clinical studies may indicate the need for bioavailability studies on the (presumably changed) food or food additive. Results of these studies will enable meaningful comparisons to be made among clinical studies performed with different formulations of the test substance. When

the petitioner intends to market a family of formulations and only a limited number of the formulations will be tested in clinical studies, petitioners should be prepared to demonstrate that the test compounds are fully representative of the family of formulations intended for marketing, particularly with respect to questions of safety.

4. Submitting Reports of Clinical Studies on Foods and Food Additives to CFSAN

In submitting reports of clinical studies to CFSAN, particular emphasis should be placed on clear and concise: 1) statement of study objectives, 2) description of protocols, and 3) presentation of significant findings. Presentation of the results of a series of clinical studies on an proposed food additive should be scientifically logical and should specify the order in which the studies were conducted.

Early, relatively short-term clinical studies include tolerance studies. In reporting the results of tolerance studies, information on dose schedules and range of doses should be included. For relatively short-term clinical studies, the following questions should be answered in determining the safety of the proposed additive:

- What are the absorption, metabolism, tissue deposition, and major routes of excretion of the food or food additive?

- What is the half-life of the food or food additive in the human body? (Analysis of turnover and of other pharmacokinetic parameters of the test substance or its metabolites in various physiological compartments may aid in the interpretation of the results of toxicity studies.) (see **Chapter V B**);

- How may interactions between the food or food additive and nutrients or medications compromise the availability of any of these substances?

- How does the food or food additive affect the function of human organs and organ systems?

- What are the possible adverse reactions to the food or food additive in the general population of individuals who are likely to use the substance and in special (more sensitive) populations?

Reports on relatively long-term clinical studies should emphasize specific organ or organ system responses to the food or food additive and nutrient imbalances that occur with chronic use of the food or food additive.

Finally, the safety of a food or food additive may continue to be monitored after the substance has been approved. This can be accomplished by further clinical testing or by establishing a surveillance system and documenting adverse reactions to the food additive. The need for such a system is expected to vary with the nature and use of the approved food additive. Clinical testing and surveillance also may be useful in establishing the safety of expanded uses of the food or food additive or the safety of an altered food or food additive; these changes may occur as the result of changes in patterns of food consumption or food processing.

5. Appendix A

The following principles are general guidelines for institutional review of, and conformed consent of subjects for, clinical studies. Additional information can be found in the references for this chapter.

a. Principles of Institutional Review

- An Institutional Review Board must be composed of no fewer than 5 persons from various backgrounds to assure complete and adequate review of clinical research activities commonly conducted by the institution. In addition to possessing the scientific competence necessary to review such institutional activities, the Board must be able to evaluate research applications and proposals in terms of

institutional commitments and regulations, applicable law, standards of professional conduct and practice, and community attitudes.

- No member of a Board shall be involved in the initial or continuing review of an activity in which he has a conflicting interest, except to provide information requested by the Board.

- No Board shall consist entirely of persons who are officers, employees, or agents of, or are otherwise associated with the institution, apart from their membership on the Board.

b. Principles of Informed Consent

All subjects in a clinical evaluation are entitled to:

- a fair explanation of the procedures to be followed and the purposes of the procedures, including identification of any procedures that are experimental;

- a description of attendant discomforts and risks that may be reasonably expected;

- a description of benefits they may reasonably be expected;

- disclosure of appropriate alternative procedures that may be advantageous to the subject;

- an offer to answer any inquiries concerning the procedure; and

- instruction that the subject is free to withdraw his consent and discontinue participation in the project at any time, without prejudice to the subject.

References

1. Anonymous (1979) Refusal to approve the application (21 CFR 314.111 Section A5ii) Statement concerning adequate and well-controlled clinical investigations. *Fed.Reg. (April 1) 107-110.*

2. Anonymous (1988) Protection of human subjects (21 CFR Part 50) *Fed Reg. (April 1) 215-229.*

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4. American Academy of Pediatrics Committee on Nutrition [AAPCN] (1988) In, Clinical Testing of Infant Formulas with Respect to Nutritional Suitability for Term Infants. Prepared under FDA contract 223-86-2117. *pp.1-36.*

5. American Academy of Pediatrics Committee on Nutrition [AAPCN] (1987) Guidelines for the clinical evaluation of new products used in the dietary management of infants, children and pregnant women with metabolic disorders. A report by the Task Force on Clinical Evaluation of Products for Metabolic Disorders. Prepared under FDA contract 223-82-2393. *pp.1-53.*