FOOD ADVISORY COMMITTEE MEETING ON INFANT FORMULA

Q1 Charge and Questions

This Food Advisory Committee is being asked to comment on the appropriateness and completeness of a general science-based set of guiding principles for clinical studies used to evaluate a particular infant formula's ability to support normal physical growth in an infant population.

The guiding principles were compiled from protocol recommendations that FDA included in its 1996 proposed rule[1] and from an expert report prepared for the U.K. Department of Health relative to "Nutritional Assessment of Infant Formulas"[2]

Additionally, this Committee is being asked to provide specific guidance to FDA on interpreting and using clinical studies that present challenges in interpretation when evaluating a particular infant formula's ability to support normal physical growth under the formula's intended conditions of use.

Specific questions for the Committee include:

- In evaluating the ability of a particular formula to support normal physical growth when consumed under the intended conditions of use, is it appropriate to generalize the results from clinical studies performed in one population group to a different population group, the latter being the population group for which the infant formula is intended? In answering this question, consider studies performed using
    - preterm infants for use by term infants (and vice versa); and
    - healthy infants for use by infants with underlying metabolic and disease conditions (and vice versa).

- In evaluating the ability of a particular infant formula to support normal physical growth when consumed under the intended conditions of use, is it appropriate to generalize the results from clinical studies that used a test infant formula that differs from the infant formula intended for market? When answering this question, consider clinical studies

[1] Proposed Rule: Current Good Manufacturing Practice, Quality Control Procedures, Quality Factors, Notification Requirements, and Records and Reports, for the Production of Infant Formula, 61 Fed. Reg. 36154 (July 9, 1996).

[2] Department of Health "Guidelines on the Nutritional Assessment of Infant Formulas: Report of the Working Group on the Nutritional Assessment of Infant Formulas of the Committee on Medical Aspects of Food and Nutrition Policy," Report on Health and Social Subjects 47 (1996).

conducted using, for example, a test formula that differs in protein source and amount from the formula that is intended for market.

- In evaluating the ability of a particular infant formula to support normal physical growth when consumed under intended conditions of use, is it appropriate to generalize the results from clinical studies that used a test formula designed for one population and tested in that population to a second formula designed for a second population? When answering this question, consider clinical studies performed using a preterm infant formula consumed by preterm infants when the infant formula intended for market is a term formula for use by term infants (and vice versa).

- Is it appropriate to conclude that a new infant formula supports normal physical growth under its intended conditions of use when there are differences in adverse events between the test and control groups, which raise clinical concerns, but the study was not powered to detect?

- Is it appropriate to conclude that a new infant formula supports normal physical growth under its intended conditions of use when there are large differences in attrition rates between study groups?

Tentative Guiding Principles for Clinical Studies

a. Appropriate pre-clinical studies should be performed for previously untested components of infant formula (COMA).

b. A pilot study should be considered to provide the information necessary to design an adequate study (COMA).

c. The study protocol should:
    i. Describe the scientific basis and objectives of the study (FDA);

    ii. Describe the planned control and treatment feeding regimens (FDA);

    iii. Describe the entrance criteria used to enroll infants in the study (FDA);

    iv. Describe the method of randomization used for the assignment of infants to feeding groups (FDA). In clinical trials, random allocation of infants to study groups should be used to minimize bias (COMA);

    v. Describe the collection of specific measurements and other data (FDA). Outcome measures should be justified as relevant to the modification under test (COMA);

    vi. Describe the methods used to limit sources of bias (FDA);

    vii. Describe the planned methods of statistical analysis (FDA);

    viii. Describe the necessary qualifications and experience of investigators (FDA). The clinical investigator must be scientifically and professionally competent and must be aware of the principles and objectives of the trial (COMA);

    ix. Be reviewed and approved by an Institutional Review Board (IRB) in accordance with Part 56 of the regulations. The manufacturer shall establish procedures to obtain written informed consent from parents or legal representatives of the infants enrolled in the study in accordance with part 50 of the regulations (FDA; COMA);

    x. Explain how the study population represents the population for which the new infant formula is intended (FDA). All

infants in studies should be characterized with regard to factors known to influence the outcome measures (COMA);

xi. Explain how the study addresses the intended conditions of use of the formula (FDA). Outcome measures should be defined specifically for testing prior hypotheses (COMA);

xii. Describe the sample size calculations and the power calculations and the basis for selecting the sample size and study design (FDA). Studies should be designed to include adequate numbers of participants, allowing for possible withdrawals of infants. Studies should be designed to have the statistical power to detect important effects on important outcomes, allowing for possible withdrawals of infants (COMA);

xiii. Describe the plan to identify and evaluate any adverse effects (FDA). Arrangements for dealing with abnormalities found during the study should be in place from the outset. The researchers should agree on the definitions of abnormality to trigger action when scrutinizing the results from individual participants (COMA);

xiv. Describe the quality control procedures used to ensure the validity and reliability of the measurements collected (FDA). The measures chosen should be assessed for their accuracy, reproducibility, feasibility, contribution to safety assessment … (COMA). The results of laboratory analysis should be monitored through a quality assurance scheme (COMA);

xv. Describe and compare the composition of the test and control formulas (FDA);

xvi. Describe the basis upon which the test formula is appropriate for use in evaluating the formula that the manufacturer intends to market, if the test formula is not identical to the formula that is intended to be marketed in the United States (FDA).

d. Where possible, investigators should be blind to the allocation of test and control formulas to minimize observer bias (COMA).

e. The need for continuing follow-up to two years of age or beyond, and the consequent ethical and practical implications, should be

considered in all studies. Longer-term post marketing surveillance may be needed to confirm the nutritional effects and safety of changes which have been introduced. When designing studies for longer term follow-up, early baseline measurements, for example, head circumference or blood levels of vitamin D, may be needed to interpret the significance of later observations. Ideally, studies should be designed with the option of longer term follow-up, even if it is not intended to pursue this in the first instance (COMA).

f. There should be common features in the design of studies so that results from several different studies can be assessed together (COMA).

Conduct of the study

g. Studies should comply with the principles of Good Clinical Practice and Good Laboratory Practice (COMA).

h. Data on all participants recruited should be as complete as possible whether or not they finish the study (COMA).

i. Data, in accord with the protocol, should be collected from all individuals who have been invited to take part, although realistically, for infants who did not finish the study, information is likely to be limited to participant characteristics. Where a study is incomplete for reasons such as changing the feeding regimen, outcome measures such as weight might continue to be recorded. The value of even limited data about infants who are invited, but who refuse to participate allows the investigation to assess the extent to which the sample is representative of the whole population and the findings can be generalized (COMA).

j. The possibility of unpredicted adverse outcomes should be addressed by adequate clinical monitoring of the participants to detect adverse outcomes and by independent scrutiny of the accumulating data. It is important to monitor the participants clinically throughout the study, and the accumulating data should be scrutinized to pick up unexpected adverse effects. If this is undertaken by the investigators, early trends of uncertain significance may bias later observations. Instead, a data monitoring committee convened by, but independent of, the investigators should be responsible for assessing the significance of adverse outcomes which have been observed and of advising the study team if there is a risk to the participants. Treatment may

be indicated or the protocol for the study may have to be amended, or the study may need to be terminated (COMA).

Data handling

k. Results from clinical studies of infant formula, including those part-completed which have been abandoned and those not showing the expected or desired outcomes should be published. It is unethical not to analyze the results of research on human volunteers. All data should be analyzed and offered for review and publication. Negative results make a valid scientific contribution and protect future infants from being subjected to the same investigation. If the study gives results of uncertain significance, it is still worth reporting as it is essential to outline the limitations of the study to avoid misinterpretation. If studies are discontinued before they are complete, the researchers should attempt to make known any observations that have been collected, especially where these have contributed to the study being abandoned. There is a particular responsibility to inform if adverse factors were so worrying that to continue might place infants at risk. It is also worth describing reasons for halting a study when these are on methodological grounds. A suitable way to communicate the outcome of stopping a study prematurely might be in a letter to a professional journal (COMA).

l. The statistical power of the study should be stated and the confidence limits of differences observed should be presented (COMA).

m. The original records, with protection of the participants' confidentiality, should be preserved wherever possible and an anonymized data archive should be made publicly available (COMA).