MINUTES
of the
FOOD ADVISORY COMMITTEE
meeting on

Infant Formula

April 4-5, 2002

Greenbelt Marriott
Greenbelt, Maryland

Members present: Cutberto Garza, M.D., Ph.D., Chair; James Anderson, Ph.D.; Robert D. Baker, M.D., Ph.D.; Francis Fredrick Busta, Ph.D.; Scott Denne, M.D.; Goulda A. Downer, Ph.D., R.D., C.N.S.; Johanna Dwyer, Ph.D.; Annette Dickinson, Ph.D.; James E. Heubi, M.D.; Joseph H. Hotchkiss, Ph.D.; Thomas J. Montville, Ph.D.; Laurie J. Moyer-Mileur, Ph.D., R.D., C.D.; Robert M. Russell, M.D.; Madeleine J. Sigman-Grant, Ph.D.; Virginia A. Stallings, M.D.; Patti Thureen, M.D and Brandon Scholz.

Members absent: Crawford, Levitz, Sandy Miller (?Mentioned in comments?)

Invited consultant: Peter Garlick, Ph.D., Department of Surgery, Health Sciences Center, Stony Brook, NY

Invited NIH liaison: George Giacoia, M.D., National Institute of Child Health and Human Development, Program Director, Developmental and Pediatric Pharmacology and Pediatric Pharmacology Research Unit Network, Rockville, MD

Invited special industry liaison: Roger Clemens, DrPH., Director, USC School of Pharmacy, Laboratory for Research and Services in Complementary therapeutics, University of Southern California; Annette Dickinson, Ph.D., Vice President, Scientific and Regulatory Affairs, Council for Responsible Nutrition

Food and Drug Administration (FDA) representatives: (Center for Food Safety and Applied Nutrition – CFSAN) Constance J. Hardy, R.D., M.S.; Linda Hayden (retired), Executive Secretary for meeting; Elizabeth A. Yetley, Ph.D., Office of Special Nutritionals; Christine Taylor, Ph.D., Administrator

Public speakers: Pamela Anderson, Ph.D., Director, Regulatory Affairs, Ross Product Division, Abbott Laboratories; Susan E. Carlson, Ph.D., professor of Dietetics and Nutrition and Pediatrics, University of Kansas Medical Center; Robert Gelardi, President, Infant Formula Council; James Hansen, M.D., Ph.D., F.A.A.P., Mead-Johnson, Co.; Michael Kaplan, M.D., Chair of Pediatrics, Evans/Northwestern Health Care; and Eric L. Lien, Ph.D., Vice President, Research and Development, Wyeth Nutrition

Summary Conclusions

The purpose of the meeting was to address four questions posed by the FDA regarding the appropriateness and completeness of a general science-based set of guiding principles for clinical studies that can be used to evaluate a particular infant formula's ability to support normal physical growth in an infant population.

A general question was asked during the initial discussion. The Committee was not asked to reach a consensus on this general question, but to begin the discussion, which will be continued at two subsequent meetings. To begin the discussion, the six general principles in the Guidelines on the Nutritional Assessment of Infant Formulas report by the Working Group on the Nutritional Assessment of Infant Formulas of the Committee on Medial Aspects of Food and Nutrition Policy (COMA Report) were used as a framework to begin the discussion. Each point was discussed twice, once as the principles relate to safety of infant formula, and the second time as the principles relate to efficacy. The resulting discussion points will be used to formulate the agenda for two subsequent meetings, at the last of which members will be asked to develop a consensus for the FDA. The general question was defined as:

> What components constitute an appropriate and complete general science-based set of guiding principles for clinical studies used in the context of providing assurances that a particular infant formula supports normal physical growth under its intended conditions of use?

Each member of the Committee was asked to provide an opinion on, and a rationale for, three additional questions, defined as follows:

1. Is it appropriate to generalize the results from clinical studies not done under intended conditions of use to different conditions of use:
   --One population to another?
   --One product to another?
   --Combination of above (e.g., preterm to term, healthy to diseased)?
2. 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 that raise clinical concerns, but the study was not powered to detect?
3. 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?

Regarding question #1, the majority of the Committee members said that, presumptively, the answer was no, it is not appropriate to generalize the results from clinical studies not done under intended conditions of use to different conditions of use. Several members provided for exceptions that would be determined by a review panel or a set of criteria to be determined. A majority of the members also agreed that a clinical study should be designed in consultation with the FDA and/or a review panel before the study commences. Several members also suggested that it would be appropriate during the preview stage for the study's sponsor to state that the results would be used to generalize to a different population or product.

Members stated that both adverse events and attrition rates, addressed in questions #2 and #3 respectively, did have an impact on study results and should be analyzed to determine the impact on the study outcome. A majority of the members stated that an independent panel of experts was needed to determine the extent of the impact adverse events and/or large differences in attrition rates between groups have on study data. All members agreed that the FDA should receive information on adverse events and a report on the causes of attrition rates, if possible, along with other data used to assure that an infant formula supports normal physical growth in the intended infant population.

Agenda

The Food Advisory Committee Chair, Dr. Cutberto Garza, convened the meeting at 9:03 a.m., Thursday, April 4, 2002. After welcoming all present and asking members and invited guests to introduce themselves, Dr. Garza explained the new structure for the Committee. The Committee is now a parent committee comprised of an ad hoc task force and chairs of the sub-standing committees. There are four sub-standing committees: Dietary Supplement, chaired by McGwire; Contaminants, chaired by Dr. Frank Busta; Bio Technology, chaired by Dr. Archer; and Additives and Ingredients, no chair at present time. The full Committee is scheduled to meet three times a year.

Dr. Garza noted that there was an influx of new members, and proceeded to record the appointment of seven new voting members: James Anderson, Ph.D.; Robert D. Baker, M.D., Ph.D.; Scott Denne, M.D.; James E. Heubi, M.D.; Laurie J. Moyer-Mileur, Ph.D., R.D., C.D.; Virginia A. Stallings, M.D.; and Patti Thureen, M.D.

No conflict of interest was noted for any of the committee members. Dr. Garza noted that the agenda asked the committee to address general matters only, thus there would be no unique or distinct effect on members' financial interests.

Dr. Garza then asked the invited guests to disclose any possible conflicts of interest. Dr. George Giacoia, Program Director, Developmental and Pediatric Pharmacology and Pediatric Pharmacology Research Unit Network, National Institute of Child Health and Human Development noted that he had been the project officer for interagency funding for _____ for resource guidelines, but that the agreement had been cancelled.

Following housekeeping announcements, Dr. Garza introduced Christine Taylor from the FDA who provided an introduction to the charge to the Committee. She was joined by Dr. Elizabeth A. Yetley, Office of Special Nutritionals, FDA, who introduced the guiding principles that the Committee was asked to consider.

Dr. Garza, noting that the six public speakers were present, amended the agenda to hold the Open Public Hearing next for the convenience of the speakers and the FDA. Robert Gelardi, President, Infant Formula Council, identified five critical issues in the current process for bringing a new infant formula to market. Susan E. Carlson, Ph.D., professor of Dietetics and Nutrition and Pediatrics, University of Kansas Medical Center, discussed findings from five clinical studies that involved feeding ordinary formula compared to an experimental formula

differing only in the addition of LCPUPA, either doscosahexaenoic acid (DHA) or arachidonic acid (ARA) to preterm or term infants. Michael Kaplan, M.D., Chair of Pediatrics, Evans/Northwestern Health Care and a consultant for Wyeth Laboratories, spoke of a continuum of changes that affect premature to term infants and the affect this continuum has on the generalization of clinical study data. Eric L. Lien, Ph.D., Vice President, Research and Development, Wyeth Nutrition, addressed the generalization of data, saying that data from clinical studies may be generalized from preterm to term infants as part of a larger body of safety and efficacy data and formula matrix concerns, including composition and bioavailability. Pamela Anderson, Ph.D., Director of Regulatory Affairs, Ross Product Division, Abbott Laboratories, introduced the decision-tree analysis process used by Abbott Laboratories to determine the generalizability of clinical study data. James Hansen, M.D., Ph.D., F.A.A.P., Mead-Johnson, Co., supported the generalization of clinical study data, noting that study designs integrate safety and efficacy, and take into account major and minor changes in formula matrices. A discussion followed during which Committee members asked questions of the speakers.

Following a recap of the charge and questions by Dr. Taylor, Dr. Garza convened a discussion among Committee members on the principles addressed in the general question before the Committee. A subsequent discussion was held on the three questions that the Committee was asked to come to a consensus on. Dr. Garza recessed the meeting at 4:30 p.m.

Dr. Garza reconvened the Committee at 8:30 a.m., Friday, April 5, 2002. Following a brief recap of the questions and charge to the committee by Dr. Taylor, discussion ensued on the three questions. Dr. Garza then asked each individual member to present his or her opinion and a rationale for each of the three questions on which the Committee had been asked to reach a consensus. Beginning with the invited guests, Dr. Garza asked each individual to respond to each of the three questions. The meeting was adjourned at 11:30 a.m.

Presentations: FDA

Christine Taylor provided an overview of the 1980 Infant Formula Act, which recognizes infant formula as unique to other foods because it is the sole source of nutrition for a vulnerable population. The law amended the Federal Food, Drug and Cosmetic Act to include section 412, which required the FDA to adopt regulations implementing the Act, including regulations on quality control procedures, labeling, recall procedures, and the bioavailability of nutrients and maintenance of level of potency within the formula.

The Act was amended in 1986 to include CGMPs, audit and record keeping, and recall requirements adopted by the FDA to prevent children "from ever again being threatened by defective baby formula."[1] The 1980 Act and 1986 amendment created infant formulas as a special class of foods.

Sections 409 and 201 address the safety of specific ingredients and the product's intended use. Under these sections, each ingredient added to food, including infant formula, must either be approved for \ use as a food additive, or be generally recognized as safe (GRAS) for its intended

use. Safe or safety means that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use.

As provided for in the Act, the FDA must be notified 90 days prior to the date the manufacturer intends to market a new infant formula. Within the 90-day notification period, the FDA may oppose the marketing of the formula, ask for additional information, or choose not to respond. If the FDA opposes the formula, the manufacturer may still market the product. There is no checklist of data or materials that manufacturers must provide the FDA during the 90-day notification period. The Act makes it incumbent on the manufacturer to provide adequate assurances to the FDA that the new infant formula meets the quality factors for the normal physical growth of infants.

A new infant formula is defined as 1) an infant formula manufactured by a person that has not previously manufactured an infant formula, and 2) an infant formula manufactured by a person that has previously manufactured infant formula and in which there is a major change in processing or formulation from a current or any previous formulation produced by such manufacturer. A major change is defined as "any new formulation, or any change in ingredients or processes where experience or theory would predict a possible significant adverse impact on level of nutrients or availability of nutrients."[2]

The quality factors pertinent to a new infant formula include assurances that the final product, as formulated, has the required nutrients, is produced under proper manufacturing protocol and analysis for required nutrients, and will provide nutrients in a biologically optimal manner (bioavailability) to promote normal healthy growth.

Dr. Taylor then presented the charge to the committee with the four questions that the FDA asked the Committee to address. The FDA is seeking discussion and input on guiding principles for the formulation of an information forum relative to section 12. Specifically, what principles the FDA should use when evaluating manufacturer data to assure that it meets the standards for normal physical growth of infants.

Dr. Elizabeth Yetley addressed the most salient points for quality assurance as: science-based, clinical studies data, and the formula's ability to support normal physical growth—the common measure of nutritional adequacy. Dr. Yetley asked for specific guidance on the appropriateness of generalizations from study conditions to market conditions, e.g., one population to another, one product to another, and additional ways to measure nutritional adequacy that would take into account host and product factors, such as a specific infant population's physiological requirements.

Dr. Yetley explained that the FDA is looking for an optimal range of nutrients based on advocacy and safety from a biological perspective. An optimal range is needed, she explained, because either too little of a nutrient or too much can have an adverse effect, creating risk for the infant population. Compounding the difficulty of achieving an optimal range of nutrients is the shelf life of a product. A product's effectiveness over its shelf life is determined by the ingredient source, interaction between ingredients, formulation, and processing technique. She noted that formulas are adjusted to account for these shelf-life factors, so a formula used at the

end of its shelf life will have a different formulation than one used early in its shelf life, ultimately delivering different nutrient levels to infants.

Dr. Yetley asked the Committee to determine a set of principles that the FDA could use as a common basis for discussion and for evaluating a manufacturer's assurance data. She asked that these guiding principles provide a basis for interpreting clinical study data, particularly in regard to adverse events and attrition rates between study groups; sample size and power calculations within studies; and overall study design.

Dr. Garza asked if there was a formal definition of normal physical growth. Dr. Yetley responded that there was not. Normal physical growth now is determined through measurements made at a doctor's office, which then are compared to national standards. She also noted that normal physical growth in formula-fed infants is compared generally only to other formula-fed infants, that there is little data comparing normal physical growth of formula-fed infants to breast-fed infants, and that studies currently follow only the first 12-months of life.

Dr. Yetley presented the four questions the Committee was asked to address.

General Question:

> What components constitute an appropriate and complete general science-based set of guiding principles for clinical studies used in the context of providing assurances that a particular infant formula supports normal physical growth under its intended conditions of use?

Specific Questions for Consensus:

1. Is it appropriate to generalize the results from clinical studies not done under intended conditions of use to different conditions of use:
   --One population to another?
   --One product to another?
   --Combination of above (e.g., preterm to term, healthy to diseased)?
2. 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 that raise clinical concerns, but the study was not powered to detect?
3. 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?

Public Hearing Presentations:

Robert Gelardi, President, Infant Formula Council, identified five critical issues in the current process for bringing a new infant formula to market: 1) science-based quality factors developed with input from medical-science community and structured within a framework that is not overly restrictive; 2) clinical studies that are scientifically, ethically, and medically sound; 3) acknowledgment of the manufacturer's scientific knowledge base; 4) generalization of findings

based on scientific merit and relevance; and 5) a pre-market notification process in which manufacturers work with the FDA to meet the needs of infant health.

Susan E. Carlson, Ph.D., professor of Dietetics and Nutrition and Pediatrics, University of Kansas Medical Center, discussed findings from five clinical studies that involved feeding ordinary formula compared to an experimental formula differing only in the addition of LCPUPA, either doscosahexaenoic acid (DHA) or arachidonic acid (ARA) to preterm or term infants. In the five trials, of which she was the PI, Dr. Carlson summarized that infants who benefit from dietary DHA also may need ARA because the enzymes for synthesis are identical through the delta-5 desaturase step that forms ARA and elcosapentacnoic acid (EPA).

The clinical studies were done in a number of different geographical locations, in populations of infants whose mothers have different cultural patterns of food intake and bear their children at different ages, in infants born early in the third trimester of gestation, and infants born at term, and with DHA and ARA from different sources [egg phospholipids and triglycerides, fish oils (low and high EPA) and single-cell oils]. Because of this (not despite this), she concluded that DHA and ARA together are unlikely to adversely influence growth of either preterm or term infants. In summary, Dr. Carlson stated that preterm infants, but not term infants, have been shown to have lower growth when fed formula with DHA compared to a commercial formula without DHA. Preterm infants fed DHA and ARA have not been shown to have lower growth compared to a commercially available formula. From that data, she concluded that preterm infants fed DHA and ARA can be generalized to term infants for the purpose of growth as an outcome. On the other hand, she said, one may not generalize data from term studies to studies of healthy preterm infants, because term infants fed DHA without ARA did not show lower growth, but preterm infants did.

Based on her clinical study experience, Dr. Carlson stated that the ability to generalize data is never completely possible from any single-population study, however large. Even seemingly identical studies carried out several years apart may yield a different outcome, i.e., information gained from the first study may not be generalized to the second. This is in part because scientists understand that uncontrolled factors, both known and unknown, may influence the study outcomes, the scientific community expects that an intervention will be tested in a variety of populations before conclusions about a finding can be accepted.

Michael Kaplan, M.D., Chair of Pediatrics, Evans/Northwestern Health Care and a consultant for Wyeth Laboratories, spoke of a continuum of changes that affect premature to term infants and the affect this continuum has on the generalization of clinical study data. Dr. Kaplan proposed that normal physical growth standards should compare formula-fed infants to breast-fed infants of the same gestational age. He cited the fact that infants' physiological requirements change on a weekly basis, with the needs of a preterm infant at 23 weeks significantly different than those of a preterm infant at 33 weeks as an example, with the 33-week infant nearing the nutritional needs of a full-term infant. For these reasons, Dr. Kaplan stated that he was not comfortable generalizing term to preterm, but was comfortable generalizing preterm to term.

Eric L. Lien, Ph.D., Vice President, Research and Development, Wyeth Nutrition, addressed the generalization of data, saying that data from clinical studies may be generalized from preterm to

term infants as part of a larger body of safety and efficacy data. He cited GRAS, systematic reviews, comparisons to nutrients found in human milk, commercial experience, and the history of use in term and preterm infant formulas worldwide as factors that support the generalization. The formula matrix also contributed to the ability of the data to be generalized, according to Dr. Lien. He cited four concerns regarding the formula matrix: 1) composition of the formula limits potential for nutrient-nutrient interaction; 2) known bioavailability in preterm and term matrices; 3) experience of the manufacturer; and 4) clinical assessment across multiple matrices and manufacturers.

Pamela Anderson, Ph.D., Director of Regulatory Affairs, Ross Product Division, Abbott Laboratories, introduced the decision-tree analysis process used by Abbott Laboratories to determine the ability of clinical study data to be generalized. Noting that Abbott Laboratories cannot give a definitive yes or no to the question of generalization, Dr. Anderson explained that Abbott uses a decision analysis approach, which may produce a different conclusion for different nutrients, ingredients, or compounds.

The approach breaks down ingredients and nutrients into five general categories: 1) standard nutrients—the 29 nutrients required by the Infant Formula Act; 2) other nutrients that may be added, but are not required; 3) non-nutritive components of breast milk that may be added to formula, but are not required; 4) novel compounds or ingredients that are ill defined or thought of; and 5) other food additives. It also looks at safety, bioavailability, growth, and efficacy. When making an analysis, Anderson said that Abbott assesses the study data based on all the factors in the matrix as well as its knowledge and experience in ingredient sourcing, product development, food processing, sterilization, understanding of pediatric nutrition, and the protocol and quality of the study.

James Hansen, M.D., Ph.D., F.A.A.P., Mead-Johnson, Co., supported the generalization of clinical study data, noting that study designs integrate safety and efficacy, and take into account major and minor changes in formula matrices. Dr. Hansen stated that trial design requires input from medical experts as well as the academic community, and that the objective is to access expertise, work collaboratively, and maintain standards. He differentiated between major and minor changes to infant formula when determining whether data may be generalized from product to product, stating that a major reformulation requires clinical study, whereas a minor reformulation may be made on scientific rationale without clinical study.

Discussion with Public Hearing Speakers

The Committee questioned the speakers at length, and used the question and answer period for extended discussion among members.

Major topic areas of discussion and issues raised and points made were the following:

Physiological vulnerability. Preterm infants have different nutritional requirements and physiology than term infants, and preterm infants' needs change as they grow and mature. The general measurement for normal physical growth is weight gained, though normal weight gain in preterm infants is significantly greater than that of term infants. In addition, it was noted that

preterm infants are by nature not "healthy" infants by the same definition as term infants. Studies generally exclude preterm infants that have medical issues, including the very small (400 to 500 grams), leaving that population of infants understudied.

Study population. Most clinical studies are conducted with preterm infants because they are in a controlled setting that simplifies the monitoring of nutritional intake, weight gain, and other study factors. Term infants are better able to control their intake, and the care provider also may influence the quantity and type of nutrition delivered, making a controlled study of term infants more difficult.

Study design. Clinical study protocol must include the healthiest of babies—those that can tolerate oral feeding and are not receiving drugs or other interventions. The infants must encompass a range of ages, with the same weights in both the study and control group. In addition, the study must strategize between weight ranges and be powered to account for anticipated attrition rates. Because many studies now are distributed among numerous institutions, the practices of the institutions may affect the outcome, requiring the studies to be blind and randomized.

Data relevance. Differences in attrition rates between groups and adverse events both have the potential to affect the relevance of the clinical study data, particularly when a significant difference occurs between the study and control group. Reasons for attrition should be noted when known and provided with the data. Adverse events should be analyzed as they occur. The definition of an adverse event may be different for a study of infants than is generally acceptable in clinical studies. In a clinical study for infant formula, an adverse event may be diarrhea, which in other studies may be considered insignificant. Adverse events should be monitored continuously for safety in addition to statistical significance.

Discussion by Committee of General Question Offered by FDA

Dr. Garza proposed that the recommendations in the Report of the Working Group on the Nutritional Assessment of Infant Formulas of the Committee on Medical Aspects of Food and Nutrition Policy (COMA Report) be used as a strawman to stimulate and structure the discussion on what components should constitute an appropriate and general, science-based set of guiding principles for clinical studies used in the context of providing assurances that a particular infant formula supports normal physical growth under its intended conditions of use. Though the COMA Report recommendations were acceptable as a starting point for the discussion, members felt that they would need to be redefined and added to in order to meet the FDA's request for guidance. The COMA Report recommendations used for the purposes of the discussion are as follows:

A1. All modifications to infant formulas should be assessed nutritionally.
A2. Studies should be founded on a systematic review of relevant existing information. All such reviews should be made publicly available.
A3. At the outset of a nutritional study there should be a clear hypothesis of functional or clinical benefit with defined selection criteria and outcome measures.

A4. Infant formulas, which have been modified for other reasons than to provide a functional or clinical benefit should at the least be subjected to studies of acceptability.
A5. All studies should be interpreted in the light of outcomes of healthy infants exclusively breast-fed for four to six months, rather than the composition of human milk. In the absence of adequate data, consideration should be given to including a breast-fed reference group in studies.
A6. Reference datasets for common outcome measures for breast-fed infants should be developed.

Dr. Garza reminded members that the FDA is required to stay within the regulations of the Act, but that the Committee was able to make recommendations that it felt were appropriate, whether or not they were within the law.

A point of clarification was made that approximately five or six companies manufacture infant formula and are regulated by the FDA.

Major topic areas of discussion and issues raised and points made were the following:

Normal physical growth. This remains the necessary criteria, but whether or not it is sufficient was a point of discussion, as was the definition. Acquisition of mass was see as a primary definition, but one that did not include the implications of growth or the difference in growth rates between preterm and term infants. It was acknowledged that there are few techniques for measuring normal physical growth in infants other than mass.

Committee members acknowledged that as science evolves there may be opportunities for additional measurements, e.g., body composition, and that these should be sought out and used as they become available, providing the safety of the infants is not at risk.

The opposite of normal physical growth was defined as not gaining weight. If infants do not gain weight, safety concerns would be raised. The FDA is seeking specific guidelines from the Committee on how to analyze claims beyond normal growth.

Standards for comparison. Four of the members supported using normal physical growth of breast-fed infants as the standard of comparison for formula-fed infants. This was not supported by all members, however, with at least one noting that the normal physical growth of infants is the benchmark and that it can be measured adequately by comparing two formula-fed populations. It was noted that using breast-fed infant growth as the standard could potentially raise issues, e.g., socioeconomic, due to the strong selection bias whether or not to breast feed. One member noted, however, that UNICEF and other international study data indicate that selection bias doesn't impact infant growth.

The difficulty in designing a study involving a control group of breast-fed infants and a comparable formula-fed group was noted. Members agreed with the difficulty of designing such a study, but indicated that difficulty in design did not negate the value of the potential data and so, when indicated, should be pursued. A study of healthy term infants and the very small

preterm infants would provide benchmarks for discussion, as these two populations generally are excluded from clinical studies.

General incremental growth standards are needed. A longitudinal growth study, including heights, etc., would provide additional data to support growth measurements.

Processes for collecting growth data need to be formalized with training and a model of conduct for practitioners. Equipment also needs to be standardized, e.g., digital scales.

Weight gain comparisons in the future should study long-term obesity in formula-fed versus breast-fed infants to assess effect of formula over the long term.

Exclusion criteria. Recognized by the members as a complex issue, exclusion criteria generally seek to admit to the study only healthy infants. In the case of preterm infants, exclusion criteria admit only infants that feed orally and are not subject to any other intervention, i.e., drugs. This, by nature, means that infants who are not healthy are not studied, resulting in no data that assesses their growth on formula.

Study design. Committee members generally agreed that the design of clinical studies needs to be reviewed before the study commences, with many preferring that an independent review panel undertake the review. During the design phase, the intent to generalize data from one population to another would need to be stated, and the study would have to be shown to be sufficiently powered to account for anticipated attrition rates. The extent of transparency and a clear hypothesis also should be assessed.

Data availability. It was noted that clinical study data currently is proprietary until the formula is marketed. A Committee member proposed that data be distributed during a six-month common period during which the information may be reviewed.

Independent review panel. The question was raised about who should be reviewing clinical study designs and the data collected in order to assure new formulas meet the requirements of the Infant Formula Act, and whether or not the data can be generalized from one population to another or from one product to another. An independent review panel was proposed that would oversee all studies and notifications from manufacturers to develop a body of knowledge that encompassed all research in the field. The review panel would provide for a consistent interpretation of data and an overall view of the data that would recognize correlations between data, which are now collected and reviewed singularly in a proprietary process.

Revisions to notification process. A suggestion was made that a checklist be developed that would indicate to manufacturers the data and material necessary to submit a 90-day notification to the FDA. Though this checklist could not be enforced, the FDA would have the ability to oppose marketing a formula if the checklist is not complete. The checklist also could be used to determine if the degree of change in the new formula was major or minor. The opinion also was expressed by a member that the reason for a change in a formula should be made public, supported by the underlying science.

Major and minor changes. Several Committee members expressed an interest in requiring all new infant formulas to be assessed for nutritional as well as clinical, dietary, and chemical implications. Currently, formulas that are considered to have major changes are reviewed.

Safety vs. efficacy. The current regulations address safety and nutrition, not efficacy. Manufacturers can add components that do not have a proven benefit, provided the components do not change the nutrient delivery of the formula or jeopardize the safety of the targeted infant population. The definition of safety relates to toxicity, so that safety may not be equated with efficacy. Efficacy would require proof that all ingredients in a formula are for the benefit of the infant.

Safety is the principal guideline when a new component is introduced into a formula. If the component is not a "normal" component, i.e., a component of breast milk or one required under the Act to be present in a formula, the component is regulated by section 409 as a food additive. Safe or safety in this situation means that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use. If proven safe under this guideline, a food additive that shows no benefits to the targeted infant population could be added to formula. For example, if red dye is high in iodine and if the iodine interfered with or augmented the bioavailability of iodine in the formula, a need assessment would be required. If the additive had no effect on the bioavailability of the nutrients in the formula, then no assessment would be required under section 409.

Assessment of acceptability. There are two aspects to this assessment—functional and clinical. The functional process assesses the acceptance of the new formula by the study population. For example, infants, mothers, fathers, and caregivers will tolerate the new formula—it doesn't smell, the color is acceptable, the infant will consume it, the formula keeps well, etc. The clinical aspect assesses whether or not the physiological changes, i.e., stool pattern, are acceptable, and looks at whether the new product was developed for scientifically sound purposes, e.g., not just to make infants want to eat more so more formula is sold.

Discussion by Committee of the Three Questions on which the FDA Requested a Consensus.

Dr. Garza open discussion on the three questions on which the FDA requested a consensus from the Committee. Dr. Garza informed Committee members that they would be asked to individually state, for the record, their position on each question and provide a rationale for their decision at the session Friday, April 5, 2002.

Issues raised and points made during the discussion were the following:

Question #1: Is it appropriate to generalize the results from clinical studies not done under intended conditions of use to different conditions of use:

--One population to another?
--One product to another?
--Combination of above (e.g., preterm to term, healthy to diseased)?

Members agreed that if data were to be generalized, it could only be generalized preterm to term, but not term to preterm because of differing physiological needs. The majority of the members expressed the opinion that data should not be generalized, with few exceptions, e.g., the study was designed with the expressed intent to generalize the data from one population to another and that the intent and study design was approved by an independent review panel prior to the commencement of the study. All agreed that the data would be beneficial to a wider body of knowledge, but that it did not translate directly between populations. As an example, it was noted that preterm infants require large amounts of certain nutrients that could possibly be toxic to term infants. A study just of preterm infants would not pick up the toxicity of these nutrients in term infants.

Members agreed that a risk assessment matrix and independent review panel would provide the FDA with a framework for analyzing data on new formulas. The burden of proof would remain with the manufacturer to assure the FDA that the new formula provides for normal physical growth in the target population.

Question #2: 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 that raise clinical concerns, but the study was not powered to detect?

Three points were made early in the discussion:

—It was noted that adverse events in studies of infant formula might differ in scope from adverse events in other studies. For example, diarrhea may be considered an adverse event in an infant formula study, whereas it might be considered a side effect in another study.
—Adverse events are included in the study design. The IRB process requires that adverse events be reported and assessed for their affect of adverse events on the study as a whole, including whether or not to continue the study when adverse events occur.
—Adverse events are difficult to estimate, making it difficult to power the study to account for adverse events.

Protocols should be developed to address expected adverse events in clinical studies for both the safety of the study population and statistically to maintain the integrity of the data.

Citing the vulnerability of the population, several members stated that the safety monitor must be independent of the company sponsoring the study. It was noted that manufacturers are not adequately qualified to identify adverse events and that IRBs often have limited pediatric expertise to review and analyze adverse events. Situations also have occurred where reviews of the same study have reached different conclusions about severity of adverse events and their relevance to the study data.

A majority of the members supported the formation of an independent review board that would analyze adverse event data for severity and frequency, and statistically for the impact of adverse events on the relevancy of the data. The general opinion was that the review board should be appointed by an agency such as FDA or NIH and paid for independently of the manufacturers.

Several members agreed that the same rigors applied to drug testing should apply to formula studies. They noted the need for a set of criteria to govern the reporting of adverse events during the course of the study, not just at the end of the study as currently required.

Industry representatives stated that manufacturers are able to interpret the data on adverse events and, while many do provide the data to the FDA, they are not required to do so until post-market. As part of the Act, manufacturers must provide consumers with a toll free telephone number for reporting problems or questions with the formula. Information collected via the toll free telephone number is reported to the FDA.

Several members did not see this as adequate for post-market follow-up. They suggested instituting a "Formula Watch," similar to "Med Watch" (which does report events for formula in general), which would alert the public to adverse events as reported post-market and provide a forum for physicians and consumers to report directly to the FDA.

Question #3: 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?

It was noted that a 25-percent attrition rate is common.

The majority of the members expressed the opinion that large differences in attrition rates between study groups does have an impact on the study data. Guidelines are needed to determine the absolute attrition rate and when the study should be rendered invalid due to rate differences between the study groups.

The reasons for attrition also may have an impact on the data. While determining the reason for leaving the study may be difficult, members agreed that it is important to ascertain reasons—whether by chance, e.g., leaving the area, or because of the intervention. The majority of the members agreed that this information does have an impact on the relevancy of the study data.

The majority of the members agreed that an independent review board was needed to analyze the attrition data and determine if the reasons for attrition or the statistical differences in attrition rates would impact the relevancy of the data.

Dr. Garza recessed the hearing at 4:30 p.m. Thursday, April 4, 2002.

Dr. Garza reconvened the hearing at 8:30 a.m. on Friday, April 4, 2002. Dr. Chris Taylor presented a brief recap of the regulations and rules governing infant formula to which the FDA must adhere. Dr. Taylor reiterated that the primary purpose of the regulations and the associated quality factors is to assure that the required nutrients are in the formula, that the bioavailability of the ingredients is as required to support normal growth, and that the formula, as constituted, is safe for the target population. The purpose of the product specific quality factors is to provide assurances of the safety of the formula prior to marketing, not to find new components for infant formula.

Dr. Taylor noted that most studies submitted to the FDA for assurance purposes show the bioequivalance of the new formula to support normal growth to an existing formula, versus the beneficial aspects of the formula, such as a comparison to breast-fed infants. Dr. Taylor also noted that two-tail studies, with a comparison to normal growth in breast-fed and formula-fed infants, could be a topic of conversation at the next two public hearings as the discussion continues on the general question posed to the Committee. She said dates and times of the next two meetings will be arranged as quickly as possible and provided to Committee members.

Dr. Garza then opened the floor for discussion of the three questions prior to taking formal statements from the individual Committee members. The discussion focused on adverse events, addressed in question #2. A Committee member asked if the FDA was seeking written guidelines regarding the action to be taken with adverse events. The FDA would like guidance about determining if the data is useful or not, and how it should use the data if the available data has significant differences in clinical adverse events between the study groups. Dr. Taylor noted that there is not a checklist for manufacturers to follow when submitting pre-market data and that the FDA does not provide the assurance criteria.

The composition and design of clinical studies also was discussed with Committee members responding that the composition of the study groups should mirror the intended U.S. population, and that data collected needs to be consistent. Some studies collect only growth data—weight and measurements—others include other biochemical data. Under current quality factors, the decision of what data to collect is left to the investigator, under the direction of the manufacturer.

Seeing no further discussion, Dr. Garza began the process of asking each individual to provide his or her opinion on the three questions before the Committee. He asked that individual provide as much guidance, criteria, and rationale as possible. Dr. Garza indicated he would call on the invited guests first, in alphabetical order, and then move to Committee members.

—Roger Clemens, representing the infant formula industry:

Question #1: Results derived from clinical studies of an infant formula in preterm infants may be generalizable to products for term infants based on a studied analysis of a) the clinical trial and b) other confirmatory evidence available. Dr. Clemens provided additional information on the decision-tree analysis process introduced by Pamela Anderson, a public speaker, on Thursday, to support his opinion on this question.

Discussion: In response to questions from Committee members, Dr. Clemens said that the decision-tree process asks five basic questions that determine the validity of the study data. He offered to provide more information on the decision-tree process used by manufacturers. Dr. Clemens clarified that good medical practice incorporates clinical design and protocol, which for most studies includes infants from 30-33 weeks of age to 52 weeks of age. Regarding other evidence available, Dr. Clemens said that manufacturers look at the similarity and dissimilarity of the studies, including the exclusion criteria and gestational age when evaluating the relevance of the data.

Question #2: It is appropriate to use the data (even with adverse events) to support growth. If one is doing an appropriate power analysis for growth, the studies are not powered to detect relatively low differences in adverse events. This does not negate the power of the study with respect to supporting growth. If a difference between study groups in the number of adverse events is observed, whether or not the study is powered to detect that rate, the clinical significance of the difference must be evaluated through good medical practice.

Question #3: Our typical clinical experience suggests that the normal attrition rate in a growth study approximates 25 percent. The assessment of physical growth is relatively insensitive to attrition rate. For example, study groups with 10 percent versus 20 percent attrition rates to not have the potential to sufficiently bias the assessment of physical growth rates to change the outcome of the study.

Discussion: In response to questions from Committee members, Dr. Clemens stated his opinion that attrition rates do not impact the results of the studies; that all data are relevant. He said that all manufacturers handle differences in attrition rates differently and rely on statistical analysis to assure that the mean is not affected.

—Peter Garlick, an invited consultant from the Department of Surgery, Health Sciences Center:

Dr. Garlick made a general comment that infant formula is more like a drug than food and that regulations regarding it should incorporate more of the drug testing procedures.

Question #1: Presumptively, the answer is no to the generalization of data from one population to another because term and preterm infants are metabolically different. Studies are needed that look at both populations. FDA should review the design of studies, before implementation, when generalization is requested from preterm to term infants.

Question #2: An independent board should be set up to monitor clinical studies. An oversight board comprised of manufacturers can influence the outcome. The board would set guidelines for sample size, reporting adverse events, and so on to make the reporting more rigorous and the data more useful. A better method of reporting adverse effects post-market also is needed.

Discussion: Dr. Clemens clarified that adverse events do not have to be reported to the FDA during the 90-day notification period, and that a mandated complaint system is in place that requires manufacturers to provide consumers a toll-free number to file complaints post-market. Dr. Taylor noted that some manufacturers provide adverse event data to the FDA during the 90-day notification period and others do not.

Question #3: A higher attrition rate in one group could be the result of the formula and thus would have an affect on the data. When possible, reasons for why participants have dropped out should be obtained. Dr. Garlick recommended that studies with large attrition rate differences between groups should be referred for further analysis.

—Annette Dickinson, industry representative:

Question #1: The answer to this question must focus on the relevance of the data to other populations, with the decision-tree process possibly used as an analysis tool along with a good understanding of the nutritional requirements of preterm and term, and healthy and unhealthy infants. The manufacturer must make the case that the data is relevant as generalized. There is no simple yes or no answer to the question.

Questions #2 and #3: The manufacturer bears the responsibility for assuring the FDA that studies affected by differences in attrition rates and adverse events do not impact the relevancy of the data as a whole.

—George Giacoia, NIH liaison:

Question #1: Children are not miniature adults, thus the sample must be representative of the target population. Data from preterm studies cannot be generalized to term infants without guidelines. Study design is critical to the relevancy of the data because birth weight versus gestational age may not be relevant, and other factors, such as socioeconomic, can change outcomes.

Question #2: Adverse events need to be understood and characterized to the degree of severity before the impact of adverse events can be determined. A system is needed to replace the current voluntary system and the post-market system for reporting adverse events.

Question #3: A review is needed to evaluate the affect of attrition rates on the data. Attrition rate should be tied to the results, and the reason for attrition should be collected and used as part of the analysis.

—James Anderson, temporary voting member:

Question #1: Generalization from product to product must be determined on a case-by-case basis. Data cannot be generalized from term infants to preterm infants or from healthy to unhealthy infants. There possibly are circumstances where study data is applicable from one population to another. An advisory panel should be established that assists the FDA in determining if the data is adequate. The panel should be engaged in the process both during and before the 90-day notification period.

Question #2: Comprehensive reports of adverse events should be part of the data submitted to the FDA during the 90-day notification period. The FDA should use the advisory panel to determine the clinical significance of the adverse events data.

Question #3: Large differences in attrition rates may be from chance or the intervention, and should be part of the data submitted to the FDA during the 90-day notification period. Only compelling evidence that attrition is not related to the intervention would leave data valid. The FDA should use the advisory panel to determine the clinical significance of the attrition data, based on a cumulative body of case reviews developed by the panel. The 90-day notification period is too short using the established intent to market process.

—Robert D. Baker, temporary voting member:

Question #1: Generalization of data needs to be qualified; in general it should not be allowed because populations are not the same. The onus is on the manufacturer to show that exceptions are valid. All relevant data should be submitted to support the data. The study data is not necessarily the basis for assurance, but rather the large body of expertise and experience, including existing literature may be sufficient.

Question #2: Adverse events should be taken into account during the clinical study process and reviewed by the advisory board for relevancy.

Question #3: Attrition rates can be a statistical problem. The validity of the attrition data needs to be evaluated using statistical support.

—Scott Denne, temporary voting member:

Question #1: Presumptively, the answer is no because of physiological differences between populations; preterm infants cannot model term infants. Healthy preterm is an oxymoron. Generalization of preterm data to term would require a strong scientific reason and should be scientifically justified before the study commences with preterms.

Question #2: In general, adverse events should be assessed by an independent review panel for severity and frequency, and their overall affect on study data. A mechanism is needed for assessment.

Question #3: Differences in attrition rates should be reported with the study outcomes and evaluated by a review board. Substantial differences may mean the study is inadequate.

—James E. Heubi, temporary voting member:

Question #1: Categorically, the answer is no—data may not be generalized from population to population or product to product. An expert panel should be convened to review data; with exceptions made only for scientific reasons, such as when the physiology is the same or the process is same (for products).

Question #2: Studies should be powered to the anticipated adverse event rate. A safety board should be convened to focus on unanticipated and serious adverse events, with an additional focus on marketing.

Question #3: Differences in attrition rates should be investigated. Studies should be powered to the anticipated attrition rate. Excessive attrition would make results suspect.

—Laurie J. Moyer-Mileur, temporary voting member:

Question #1: Formula is more a drug than a food. Generalization from preterm infants to term infants and from product to product should not be allowed. Exceptions would require review by and approval from a panel of experts.

Question #2: A board should be convened to review data for severity and frequency of adverse events, with variability a concern both during the study and post-market. Guidelines are needed for adverse events in pre- and post-market situations.

Question #3: The attrition rate should be taken into account in the study design and be part of the statistical analysis. Differences in attrition rates between groups should be divulged along with the reasons for attrition.

—Virginia A. Stallings, temporary voting member:

Question #1: The goal of the process is to build a better formula. The manufacturers have an amazing safety record. It is important to note that we are not here because something happened, but because industry and FDA want to bring safe products to market. The relevance of the data is a better indicator than the generalizability of the data. This is an opportunity to revamp the system to include industry, academics, and medical professionals. A pre-review system is needed whereby the FDA, through an independent advisory panel, and industry work together to resolve concerns over study designs before they are undertaken. The independent panel would develop a body of case studies and identify areas of uncertainty quickly, without delaying the review of proposals.

Question #2: Adverse events need to be looked at carefully. An independent review panel is needed to review adverse events. With infant formula, adverse events do not have to be "severe" to warrant attention because of the GI intolerance of infants. For example, diarrhea may be an adverse event that might cause concern, whereas in another study it may be viewed as a normal side effect. A review panel is needed to identify non-serious events and to track them across studies. The post-market process for reporting adverse events should not be relied on for information.

Discussion: A discussion ensued clarifying the members' intent for an independent board. The independent board should be comprised of a variety of experts—science, statistics, pediatrics, and neonatology. The board would oversee all studies to provide an uniformity of response to FDA and industry, and build a body of knowledge. The board would see data from all sites and be able to review them for trends and problems. Industry should be excluded from the board and board members would recuse themselves when their organizations are directly involved in a study. Currently, institutions and industry have oversight boards, but it is common for studies to take place in multiple institutions, with no one board providing oversight to all. The composition of industry boards must be accepted by the FDA based on the qualifications of the members. FDA would appreciate guidelines on how an industry board's composition should affect the agency's decision on the usability of the data. Members responded that the first guideline is the safety of the infants, then randomization and protocol; additional guidelines are to be determined.

Question #3: Large differences in attrition rates must be explained. Then the FDA must determine if the difference affects the relevancy of the data.

—Patti Thureen, temporary voting member:

More studies are needed of high-risk populations. Comments should not be construed as anti-industry.

Question #1: Data should not be generalized, with few exceptions, because of the physiological differences between term and preterm infants. There is the possibility of exceptions for preterm to term if the independent board reviews the study design before it is implemented and there is adequate scientific data to support the generalization.

Question #2: This is a two-part question. Adverse events cannot keep some studies from being relevant. Strongly recommend that minor issues be addressed and monitored. Formula needs to be thought of more like a drug in clinicians' minds to get them to report post-market adverse events on toll-free number. A board is needed to review studies pre-market and another board for reports received post-market.

Question #3: Large differences in attrition rates should be reported to the FDA. Independent board could help address issues for large-scale studies involving multiple institutions.

—Francis Frederick Busta, permanent voting member:

Appreciate education received from industry, other members, and FDA during meeting.

Question #1: No generalization is 100 percent true. Relevancy of data could be ascertained if research on bioavailability is available, removing the need for clinical study. This would apply population to population and product to product.

Question #2: Adverse events should be reported and included if part of the study. Adverse events should be taken into account if they have an adverse affect on normal growth measurements.

Question #3: The statistical significance of attrition rates may not affect the relevancy of the data.

—Goulda A. Downer, permanent voting member:

Question #1: It is difficult to generalize from preterm to term because the population is physiologically different. Cannot identify studies where term can be generalized to preterm. An example of when preterm could not be generalized to term would be in the case of a formula with vitamin A in sufficient levels for preterm infants, which could cause safety concerns for term infants.

Question #2: Adverse events should be evaluated against normal growth. Adverse events should be identified and reported, and the possibility of adverse events should be incorporated in the study design.

Question #3: Study size should be adequate to account for attrition rates. Large differences in attrition rates should be analyzed for their affect on the data. Two panels should be convened, one for statistics and the other to assess the rigors of the study.

—Johanna Dwyer, permanent voting member:

Question #1: In general no, data should not be generalized from population to population or product to product. Clinical studies should be designed for the target population. At the core of this is the type of growth to be measured, taking into account the idiosyncratic views of attending physicians. Low weight/young gestational age infants need to be studied to develop basic research data. Manufacturers bear the burden for exceptions. Preterm to term infants most likely for generalization; disease to well and well to disease are problematic.

Question #2: In general no, adverse events can affect relevancy of data. Manufacturers bear the burden for exceptions. Clinical studies should be designed to take into account adverse events. An independent board should analyze adverse events. The board should review existing studies, define events, and determine what is disproportionate.

Question #3: In general no, attrition rates can affect the relevancy of the data. A 25-percent attrition rate introduces uncertainties. Studies should be powered for the anticipated attrition rate. Reasons for attrition should be determined and documented to find out if the intervention was the cause. A judgment on the relevancy of the data should be made by an independent review board.

—Joseph H. Hotchkiss, permanent voting member:

Question #1: No, data should not be generalized. This should be the FDA's default position. The onus is on the manufacturer to show that data is relevant from population to population. Mechanisms are needed for exceptions on a case-by-case basis (preterm to term and product to product). FDA is responsible for determining if the manufacturer has shown the data are relevant.

Question #2: No, it is not appropriate when adverse events occur because the adverse events may be hypothesis-related. A board is needed to analyze the affect of the adverse events and reasons on the outcome.

Question #3: If attrition rates vary between groups, the different may be hypothesis-related so it is not safe to draw the conclusion. A board is needed to analyze the affect of the attrition rates and reasons on the outcome.

—Thomas J. Montville, permanent voting member:

Question #1: Sound science says you don't extrapolate data to different conditions. A review board may be useful to review data, but ultimately, it is up to the FDA to decide.

Question #2: This is a two-part question. Adverse events must be examined and followed up on. If adverse events don't affect normal growth than the results are still valid.

Question #3: Attrition rates can affect the outcome of the study. Industry should provide data to show attrition rates are not linked to the intervention.

—Robert M. Russell, permanent voting member:

Question #1: Presumptively, the answer is no. A matrix or panel of experts is needed to recommend scoring cutoffs. Above a certain point, the data can be generalized; below it cannot. The matrix should apply to all cases.

Question #2: The impact of adverse events should be left to an independent board.

Question #3: Presumptively, the answer is no. Differences in attrition rates between groups can impact the results of studies. An independent board should review the attrition rates to determine their impact on the data.

—Madeline J. Sigman-Grant, permanent voting member:

Question #1: Presumptively, the answer is no, with the possible exception being product to product. Generalizing data makes too many assumptions—preterm is different than term in many aspects besides physiology, such as feeding frequency, caregiver attitude to feeding, and so on.

Question #2: An independent board is needed to monitor adverse events and determine if they impact the data.

Question #3: Presumptively, the answer is no. Differences in attrition rates can impact study outcomes. An independent board should analyze the affect of attrition rates on data.

Following the individual comments from the Committee, Dr. Garza asked members if they would like to amend their comments.

Johanna Dwyer, permanent voting member, endorsed Dr. Russell's suggestion of a checklist or matrix that industry could use to generalize data.

Dr. Garza thanked the Committee members and invited guests for an informative discussion. He adjourned the meeting at 11:30 a.m.