DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

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[Docket No. 1995N–0309] (formerly 95N–0309)

RIN 0910–AA04

Current Good Manufacturing Practice, Quality Control Procedures, Quality Factors, Notification Requirements, and Records and Reports for the Production of Infant Formula; Reopening of the Comment Period

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule; reopening of the comment period.

SUMMARY: The Food and Drug Administration (FDA) is reopening until [*insert date 45 days after date of publication in the* **Federal Register**] the comment period for the proposed rule published in the **Federal Register** of July 9, 1996 (the 1996 proposed rule) (61 FR 36154). The 1996 proposed rule would revise FDA's infant formula regulations in 21 CFR parts 106 and 107, and FDA is reopening the comment period to receive comment only with respect to specific issues identified in this proposed rule.

DATES: Submit written or electronic comments by [*insert date 45 days after date of publication in the* **Federal Register**].

ADDRESSES: You may submit comments, identified by Docket No. 1995N–0309 and RIN 0910–AA04, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following ways:

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NEC4

• Federal eRulemaking Portal: *http://www.regulations.gov*. Follow the instructions for submitting comments.

• Agency Web site: *http://www.fda.gov/dockets/ecomments*. Follow the instructions for submitting comments on the agency Web site.

Written Submissions

Submit written submissions in the following ways:

• FAX: 301–827–6870.

• Mail/Hand delivery/Courier [For paper, disk, or CD–ROM submissions]: Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

To ensure more timely processing of comments, FDA is no longer accepting comments submitted to the agency by e-mail. FDA encourages you to continue to submit electronic comments by using the Federal eRulemaking Portal or the agency Web site, as described in the *Electronic Submissions* portion of this paragraph.

Instructions: All submissions received must include the agency name and Docket No. and Regulatory Information Number (RIN) for this rulemaking. All comments received may be posted without change to *http://www.fda.gov/ohrms/dockets/default.htm*, including any personal information provided. For additional information on submitting comments, see the "How to Submit Comments" heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *http://www.fda.gov/ohrms/dockets/default.htm* and insert the docket number(s), found in brackets in the heading of this document,

into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Benson M. Silverman, Center for Food Safety and Applied Nutrition (HFS–850), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, 301–436–1459, e-mail: *benson.silverman@fda.hhs.gov*.

SUPPLEMENTARY INFORMATION:

I. Background

In the 1996 proposed rule, FDA proposed regulations to revise its infant formula regulations to establish requirements for quality factors and current good manufacturing practices (CGMPs), to amend the agency's quality control procedure, notification, and records and report requirements for infant formulas, to require that infant formulas contain, and be tested for, required nutrients and for any nutrient added by the manufacturer, throughout the formula's shelf life, to require that infant formulas be produced under strict microbiological controls, and to require that infant formula manufacturers implement the CGMP and quality control procedure requirements by establishing a production and in-process control system of their own design. The agency proposed these requirements to implement provisions of the Drug Enforcement, Education, and Control Act of 1986 (Public Law 99–570) that amended section 412 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 350a).

In the **Federal Register** of April 28, 2003 (the 2003 proposed rule) (68 FR 22341), FDA reopened the comment period for the proposed rule to update comments generally, and to receive new information based on three meetings of FDA's Food Advisory Committee that were held in 2002 and 2003. Among

other issues, the agency specifically requested comment on the following items: (1) Whether there is a need to include a microbiological requirement for *Enterobacter sakazakii* and, if so, what requirement the agency should consider to ensure the safety of powdered infant formulas and prevent future outbreaks; (2) what other changes in the proposed microbiological requirements would be appropriate to ensure the safety of powdered infant formula and to prevent outbreaks of illness; and (3) several questions related to quality factors, including the appropriate age for infant enrollment into clinical studies and the appropriate duration of these studies.

Significant expert consultations held since the publication of the 2003 proposed rule have provided information relevant to this rulemaking. First, a series of expert consultations has occurred related to providing scientific advice concerning *E. sakazakii, Salmonella*, and other microorganisms in powdered infant formula, as part of the Codex Alimentarius Commission Committee on Food Hygiene's (CCFH's) efforts to update the 1979 Recommended International Code of Hygienic Practice for Foods for Infants and Children (the 1979 Code). These consultations have resulted in two new reports, which we are adding to the record. The new reports are entitled "The Food and Agriculture Organization of the United Nations and the World Health Organization. *Enterobacter sakazakii* and Other Microorganisms in Powdered Infant Formula: Joint FAO/WHO Meeting 2–4 February 2004" (Ref. 1) and "The Food and Agriculture Organization of the United Nations and the World Health Organization. *Enterobacter sakazakii* and *Salmonella* in Powdered Infant Formula: Meeting Report, FAO Headquarters, Rome, Italy, 16–20 January 2006" (Ref. 2). We believe that the latter report is the most significant for purposes

of informing this rulemaking with respect to *E. sakazakii*, and it is described more fully in section II.A of this document.

In addition, new information has been provided by the Committee on the Evaluation of the Addition of Ingredients New to Infant Formula, which the Institute of Medicine (IOM) convened at the request of FDA and Health Canada, in part, to "identify tools to evaluate the safety of ingredients new to infant formulas under intended conditions of use in term infants" (Ref. 3 at 2). This consultation resulted in a March 2004 report entitled "Infant Formula: Evaluating the Safety of New Ingredients" (the IOM report) (Ref. 3). This report is described more fully in section II.C of this document.

II. Request for Comments

In the limited reopening of the comment period announced in this proposed rule, FDA is seeking comment only with respect to the following issues: (1) Whether FDA should require a microbiological standard for *E. sakazakii* for powdered infant formula of negative in 30 x 10 gram (g) samples; (2) whether FDA should not require microbiological standards for aerobic plate count, coliforms, fecal coliforms, *Listeria monocytogenes*, *Bacillus cereus*, and *Staphylococcus aureus*; (3) whether FDA should require measurements of healthy growth beyond the two proposed quality factors of normal physical growth (as measured by body weight, recumbent length, head circumference, and average daily weight increment) and protein quality; (4) whether FDA should require a measure for body composition as an indicator of normal physical growth, and if so, what measure; and (5) whether FDA should require that the duration for a clinical study, if required, be no less than 15 weeks, and commence when infants are no older than 2 weeks of age. FDA will not

consider comments outside the scope of these issues, which are discussed in more detail in the following sections of this document.

A. Microbiological Standard for E. sakazakii

In the 2003 proposed rule, we asked for comment on whether there is a need to include a microbiological requirement for *E. sakazakii*, and if so, what requirement the agency should consider to ensure the safety of powdered infant formula and to prevent outbreaks of illness (68 FR 22341 at 22342).

Some comments identified a need to include a microbiological requirement for *E. sakazakii*, but did not suggest a specific standard. Other comments stated that there is no need to establish a specific standard for *E. sakazakii*. Some of these comments asserted that the evidence does not support the conclusion that the levels of *E. sakazakii* found in unopened infant formula present a risk of harm to infants, particularly healthy, term infants. Other comments asserted that there is no need to establish a standard because the safety of infant formula would be better assured by hazard analysis critical control plans and environmental monitoring, including employing stricter criteria for the testing of indicator organisms, such as *Enterobacteriaceae*. One comment suggested that if FDA determines that microbiological specifications for future pathogens of concern are needed, it should use a mechanism for establishing these requirements, such as a guidance, that is less burdensome to publish or change than a regulation. Other comments suggested that point-of-use contamination from poor preparation practices represent the most significant risk of *E. sakazakii* infection for infants consuming formula. These comments suggested that education concerning formula preparation and handling, or additional labeling, is more likely to reduce the risk of infection than finished product testing. Some comments requested that FDA provide an

explanation of the number and sample sizes required to test finished formula product for contamination. Other comments suggest that the addition of *E. sakazakii* inhibitors to formula, such as antimicrobials inhibitory to *E. sakazakii* that are presently approved for use in foods, provide a more effective means of preventing the growth of *E. sakazakii*.

In the 2003 proposed rule, we also asked for comments on whether powdered infant formula to be consumed by premature and newborn infants should meet stricter microbiological requirements than formula intended for older infants (68 FR 22341 at 22342). With respect specifically to *E. sakazakii*, some comments said there should be a heightened standard for formulas intended for certain subpopulations of infants, including, variously, infants who are premature, of low birth weight, ill, or among a group described as vulnerable hospitalized infants. These comments argued that there should either be no standard or a lower standard for formulas intended for other infants. Other comments urged FDA to adopt the same standard for formulas intended for term infants as those formulas intended for premature infants because a risk of *E. sakazakii* infection exists in both populations. Some comments stated that FDA's request for comments on this issue is based on the incorrect premise that healthy newborns should be grouped with premature infants for purposes of risk assessment. The comments stated that the correct question is whether there should be separate standards for formulas for premature infants and formulas for healthy term infants. The comments stated that due to FDA's statutory authority under section 412(h)(2) of the act to establish terms and conditions for the exemption of formulas intended for infants who are low birth weight or who have unusual medical problems, any

effort to establish stricter microbiological requirements for these formulas should be done with a separate notice and comment rulemaking.

1. What Were the "*Enterobacter sakazakii* and *Salmonella* in Powdered Milk Formula" Meeting's (the Rome Meeting's) Conclusions Regarding a Microbiological Standard for *E. sakazakii*?

During January 16 to 20, 2006, in Rome, Italy, the Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO) convened the Rome meeting, a technical meeting on *E. sakazakii* and *Salmonella* in powdered infant formula (Ref. 2). The purposes of the Rome meeting were to consider scientific data newly available since the previous FAO/WHO technical meeting in February 2004, to evaluate a quantitative risk assessment model using these data for *E. sakazakii* in powdered infant formula, to apply this model to various risk reduction scenarios, and to provide input to CCFH for the revision of the 1979 Code. A total of 16 experts from 11 countries participated in the Rome meeting in their individual capacities, including a senior FDA scientist with expertise in microbiological contamination (Ref. 2 at vii, 1).

Recent data reviewed in the report of the Rome meeting include data concerning an *E. sakazakii* outbreak in France involving nine infants, two of which died, as well as evidence of a number of recalls of powdered infant formula contaminated with *E. sakazakii* (Ref. 2 at 8–9). These and other data reviewed in the report indicate that prevention efforts must target infants within and beyond the neonatal period (i.e., beyond the infant's first 28 days) and must target all infants, regardless of immune status (Ref. 2 at xiv). As stated in the report of the Rome meeting, based on a review of *E. sakazakii* infections worldwide, "*E. sakazakii* meningitis tends to develop in infants during the

neonatal period . . . *E. sakazakii* bacteraemia tends to develop in premature infants outside of the neonatal period with most cases occurring in infants less than 2 months of age. However, infants with immunocompromising conditions have developed bloodstream infections as late as age 10 months and previously healthy infants have also developed invasive disease outside the neonatal period" (Ref. 2 at 8). The data indicate that premature infants and those with low birth weight are at highest risk for severe infection, that infants who contract bacteremia (infection of the blood stream) have a 10 percent mortality rate, that infants with meningitis have a 44 percent mortality rate, and most infants who survive meningitis experience long-term neurological consequences (Id. at 7–8). The data also support the conclusion that there is clear evidence of causality between *E. sakazakii* in powdered infant formula and illness in infants (Ref. 2 at 5).

The experts at the Rome meeting evaluated and reviewed a risk assessment model developed to describe the factors leading to *E. sakazakii* infection in infants and to identify potential risk mitigation strategies (Ref. 2). As described in the report, among other things, the risk assessment model "provides the means to evaluate microbiological criteria and sampling plans in terms of the risk reductions achieved and the percentage of product lot rejected" (Id. at xii). In the report, the experts did not select a specific risk management approach, recommending instead that the risk assessment model be applied by risk managers within CCFH and in member countries (Id. at xiv–xv).

The model incorporates published research and extensive unpublished industry data on the prevalence of *E. sakazakii* in powdered infant formula (Ref. 2 at 44), as well as new data on consumer and hospital practices related to the use of powdered infant formula. The model estimates the risk to infants

of illness from *E. sakazakii* from contaminated powdered infant formula.[1] Using the model, relative risk reductions and lot rejection rates were projected for a total of 162 scenarios, each incorporating the following: One of nine different sampling plans, one of three mean log concentrations of *E. sakazakii*, one of two between-lot standard deviations, and one of three within-lot standard deviations. The values for the mean log concentrations and the standard deviations were based on the published and unpublished data described previously in this document. For example, the model used mean log concentration of -5, -4, and -3 mean $\log_{10}$ colony-forming units/g (CFU/g) (Ref. 2 at 46–47), while the estimated mean log concentrations in the data ranged from -2.79 to -5.24 CFU/g, with a mean of -3.84 CFU/g and between-lot standard deviation of 0.696 (Id. at 43).

As explained in the report of the Rome meeting, "the risk associated with any specific [powdered infant formula] lot is a function of the number of contaminated servings it will yield, and the ability of a microbiological criterion to reduce that risk in an effective manner is based on correctly identifying those lots with the highest level of contamination" (Id. at 50). For example, one scenario presented is for applying a sampling plan of negative in 30 x 10 g samples (n=30, s=10). In other words, under this sampling plan 30 10 g samples from various random parts of a lot of powdered infant formula, or a total of 300 g, must be negative for *E. sakazakii*. If this sampling plan is used for a lot of powdered infant formula with a mean $\log_{10}$ concentration of -5 CFU/g, a between-lot standard deviation of 0.8, and a within-lot standard deviation of 0.5, 1.4 percent of tested lots can be expected to be found positive

[1]No dose-response for *E. sakazakii* has been established. The risk assessment model assumes that illness results from one colony forming unit (CFU) of *E. sakazakii* in dry powdered infant formula at the time of preparation and calculates an exponential dose-response parameter (Ref. 2 at 16).

for *E. sakazakii* and would be rejected, and the relative risk reduction of *E. sakazakii* would be 1.21 (i.e., there would be roughly 20 percent fewer cases of *E. sakazakii* infection per year than would be the case if there were no powdered infant formula sampling plan in place). When this same sampling approach is applied to a lot of powdered infant formula with a mean $\log_{10}$ of -3 CFU/g (a substantially higher contamination level), allowing for the same standard deviations, the result is a probability that 37 percent of tested lots will be found positive and rejected and a relative risk reduction of 5.71. Thus, the more contaminated the powdered infant formula, the more the sampling can effectively reduce the risk of illness, because as the level of contamination increases, the lot rejection rate and the relative risk reduction increase. Similarly, the greater the variability in the concentration of the pathogen between lots, the greater the rejection rate within each sampling plan. Thus, if manufacturers focus on ensuring that the overall mean log concentration of the pathogen is low and that variation between lots is controlled, then the potential for rejection of the lot, and the risk of illness, are both lowered. (The model found that changing the variability within lots did not affect the projected outcomes (Id. at 49).)

2. Should FDA Require a Standard for *E. sakazakii*?

We have considered the comments received in response to the 2003 proposed rule and the information submitted in support of them, and have tentatively concluded that we disagree with those comments that oppose setting a standard for *E. sakazakii*. Some of the reasons given in the comments opposing such a standard (e.g., no evidence that levels of *E. sakazakii* in unopened powdered formula present a risk of harm to infants) no longer appear to be relevant, given the more recent data evaluated by the experts at

the Rome meeting related to the health risk posed by contamination of powdered formula (Ref. 2). In addition, the comments asserting that alternatives to finished product testing (e.g., hazard analysis critical control plans and environmental monitoring, education on formula preparation and handling, or use of inhibitors in formula) provide sufficient assurance of safety did not provide support for such assertions with respect to *E. sakazakii*. Further, newly available data, particularly the data analyzed during the Rome meeting, make it clear that *E. sakazakii* poses a significant health risk that has been linked to powdered infant formula. FDA has tentatively concluded that, rather than recommending a standard in a guidance document, as suggested by one comment, these data support establishing a requirement for a standard for *E. sakazakii* in powdered infant formula.

We have also reached a tentative conclusion, based on the scientific information currently available, about the level at which that standard should be set. Based on the data analyzed at the Rome meeting, FDA tentatively concludes that the establishment of a microbiological standard for *E. sakazakii* of negative in 30 x 10 g samples is appropriate to ensure the safety of powdered infant formula and prevent outbreaks. As described previously, FDA tentatively concludes that the standard FDA is considering in this proposed rule will prevent contamination at levels that have been shown to lead to outbreaks of *E. sakazakii*, based on the data evaluated by experts at the Rome meeting. Manufacturers would have the flexibility to decide what in-process controls, which may include environmental monitoring, are necessary to ensure compliance with the microbiological standard of negative in 30 x 10 g samples. FDA has tentatively concluded that end-product testing would provide the manufacturer with the ability to verify the effectiveness of in-

process controls and would provide FDA with the ability to determine compliance with the proposed performance standard for *E. sakazakii*. Such a standard also provides reasonable incentives for plants that need to better control *E. sakazakii*, while plants with effective control programs in place face only a minimal risk that positive sampling will necessitate lot rejection. Thus, FDA is considering a modification to part 106 (21 CFR part 106), in proposed § 106.55, that would include a requirement that manufacturers test representative samples of each lot of powdered infant formula at the final product stage, before distribution, to ensure that each lot meets the microbiological quality standard of negative in 30 x 10 g samples. FDA is also considering a modification to proposed § 106.3(g) to define "lot" as follows: "*Lot* means a quantity of product, having a uniform character or quality, within specified limits, or, in the case of an infant formula produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits."

FDA requests comment on the appropriateness of this standard and of the definition of the word "lot." FDA is requesting interested persons to submit, as part of their comments, any available scientific information and data on both the incidence of, and sampling and testing for, *E. sakazakii* in powdered infant formula. In addition to seeking comments on these tentative conclusions in response to this proposed rule, we plan to consider and address in the final rule comments already submitted concerning these matters.

3. Should the Same *E. sakazakii* Standard Apply to All Infant Formulas Covered by This Rulemaking?

We have tentatively concluded that it is not appropriate or feasible to establish a more stringent *E. sakazakii* standard for powdered infant formula that is to be consumed by premature or newborn infants. The population of infants, who may at some point in their infancy consume infant formula that is subject to the 1996 proposed rule, includes most infants who are fed infant formula, such as healthy term infants, preterm infants, low birth weight infants, ill, or hospitalized infants. The epidemiologic data, some of which is described previously in our summary of the Rome meeting, do not support the assumption that term, normal birth weight, and healthy infants—including infants who are no longer newborns—are not also at risk of adverse health consequences associated with *E. sakazakii* contamination of infant formula (Ref. 2 at 8). Furthermore, we are unaware of data that support the assumption that all preterm, low birth weight, ill, or hospitalized infants are exclusively fed formula specifically manufactured for their consumption. As a practical matter it would be difficult, except when the child is under supervised medical care, to limit the consumption by certain subgroups of infants only to a special category of formula. While it may become appropriate at some future date to propose a separate standard for formulas that are to be consumed by certain subpopulations of infants, we decline to do so at this time. Thus, we have tentatively concluded that it is appropriate to set a standard for *E. sakazakii* for infant formulas in proposed § 106.55. In addition to seeking comments on these tentative conclusions in response to this proposed rule, we plan to consider and address in the final rule comments already submitted concerning these matters.

B. Elimination of Microbiological Standards for Aerobic Plate Count, Coliforms, Fecal Coliforms, Listeria monocytogenes, Staphylococcus aureus, and Bacillus cereus

In the 1996 proposed rule, we proposed microbiological standards for aerobic plate count, coliforms, fecal coliforms, *Salmonella* spp., *Listeria monocytogenes*, *Staphylococcus aureus*, and *Bacillus cereus*. In the 2003 proposed rule, we asked for comment on what changes, if any, in the proposed microbiological requirements, other than for *E. sakazakii*, would be appropriate to provide for powdered infant formula and to ensure its safety if microorganisms are intentionally added to infant formulas (68 FR 22341 at 22342).

Several comments took issue with the proposed requirement to test each batch of formula at the final product stage for the microorganisms listed in proposed § 106.55. Other comments argued that testing for *Listeria monocytogenes* was unnecessary because this organism does not pose a significant health concern in infant formula. Several comments requested that FDA change the M value for *Bacillus cereus* to 1,000 most probable number/g (MPN/g) because there is no health concern associated with the proposed level of 100 MPN/g.

With regard to coliforms and fecal coliforms, one comment requested that FDA replace these standards with one for E. coli due to the possibility of improper interpretation of coliform and fecal coliform tests.

Regarding intentionally added microorganisms, one comment suggested that FDA exempt formulas containing these organisms from the aerobic plate count limit as long as the manufacturer employed sanitation indicative testing, such as testing for *Enterobacteriaceae*. One comment recommended an

Enterobacteriaceae standard of 3.0 MPN/g but did not provide reasoning for this standard. Other than the comment disputing the overall need for testing each batch of formula for microorganisms, no comments argued that the proposed microbiological standard for *Salmonella* spp. is unwarranted.

1. What Were the Conclusions of the Rome Meeting Regarding Microbiological Standards for Organisms Other than *E. sakazakii*?

The experts at the Rome meeting found that only *E. sakazakii* and *Salmonella* spp. in powdered infant formula had been clearly linked to illness in infants (Ref. 2 at 5). Because of this finding, they recommended standards only for *E. sakazakii* (discussed previously) and *Salmonella* spp.

With respect to the existing microbiological standard for *Salmonella* spp. in the 1979 Code of negative in 60 x 25 g samples, the experts at the Rome meeting determined that this standard is effective for protecting public health.

2. Should FDA Set Standards for Microorganisms Other than *E. sakazakii*?

FDA has considered comments submitted in response to the 1996 proposed rule and the 2003 proposed rule, as well as the report of the Rome meeting. The comments submitted on microbiological testing no longer appear to be relevant, in part, due to the changes FDA is considering to the proposed microbiological testing requirements in the 1996 proposed rule (discussed in the following paragraphs) in response to the data available from the Rome meeting. Further, FDA is aware of no marketed infant formula that contains intentionally added microorganisms and tentatively has decided not to consider requirements related to such formula, since it is not clear whether any such formula may be marketed at this time.

FDA has tentatively concluded that there is no need to require routine batch testing for microorganisms other than *E. sakazakii* and *Salmonella* spp.

We base this tentative conclusion on the following findings: (1) The data indicating both that *E. sakazakii* and *Salmonella* spp. in powdered infant formula are the microorganisms of public health concern associated with such formula, (2) the data that directly link the presence of these microorganisms to outbreaks of illness, and (3) the evidence that controls to address these pathogens in powdered infant formula will reduce the potential for infant illness. Based on this tentative conclusion, current proposed § 106.55(b) and (c) would not be finalized and proposed § 106.55(b) would be replaced with a provision that would require manufacturers to test representative samples of each lot of powdered infant formula at the final product stage, before distribution, to ensure that each lot meets the microbiological quality standard of negative in 30 x 10 g samples for *E. sakazakii* and negative in 60 x 25 g sub-samples for *Salmonella* spp.[2]

Although FDA believes that testing for aerobic plate count and *Enterobacteriaceae* can be beneficial to manufacturers in monitoring their process and production sanitation, these tests do not distinguish between pathogenic and non-pathogenic bacteria. FDA is currently proposing standards for the two pathogenic bacteria in the family *Enterobacteriaceae*, i.e., *E. sakazakii* and *Salmonella* spp., whose presence in infant formula has been linked to outbreaks of illness. Therefore, FDA has tentatively concluded, based on recent data from the Rome report, that additional batch testing, beyond the proposed *E. sakazakii* and *Salmonella* spp. standards, is not warranted at this

[2]Although the proposed standard for Salmonella in proposed § 106.55 is listed as an M value of 0, proposed § 106.55(c) states that "FDA will determine compliance with the M values listed below using the *Bacteriological Analytical Manual* (BAM)" (61 FR 36154 at 36213). Chapter 1 of the BAM states that a sampling plan of 60 x 25 g samples for *Salmonella* is appropriate for Category I foods, i.e., foods that "would not normally be subjected to a process lethal to Salmonella between the time of sampling and consumption and are intended for consumption by the aged, the infirm, and infants" (Andrews, W., et al., *Bacteriological Analytical Manual Online*, Chapter 1, available at *http://www.cfsan.fda.gov/~ebam/bam-1.html*, April 2003).

time to ensure the microbiological safety of powdered infant formula. Therefore, FDA has tentatively decided not to include requirements for testing microorganisms, other than *Salmonella* spp. and *E. sakazakii*, in the final rule.

Under the testing regimen set forth in this proposed rule, the proposed testing standards in § 106.55(c) would not be finalized. Thus, there would be no standards in a final rule for an aerobic plate count, coliform, fecal coliform test, *Listeria monocytogenes*, *Staphylococcus aureus*, or *Bacillus cereus*. Nor would there be a standard for *Enterobacteriaceae* in a final rule. However, even though batch testing would not be required for these microorganisms, the presence of these microorganisms in an infant formula reflects that the formula was prepared, packed, or held under insanitary conditions whereby it may have been rendered injurious to health and therefore is adulterated under section 402(a)(4) of the act (21 U.S.C. 342(a)(4)). FDA is interested in receiving comments, based on the FAO/WHO meetings or other scientific information, concerning its current thinking regarding the establishment of microbiological standards only for *E. sakazakii* and *Salmonella* spp. In addition to seeking comments on these tentative conclusions in response to this proposed rule, we plan to consider and address in the final rule comments already submitted concerning these matters.

C. Assessing Normal Physical Growth in Infants

In the 1996 proposed rule, FDA proposed a quality factor of normal physical growth (61 FR 36154 at 36215). Some comments to the 2003 proposed rule questioned FDA's authority to establish such a quality factor and to require a clinical study to measure physical growth. The agency is considering those comments and will respond to them in the final rule. For purposes of this proposed rule, the agency is seeking comment on certain IOM

recommendations for evaluating the safety of new ingredients in infant formula because these recommendations differed from what the agency proposed as quality factor requirements.

1. Clinical Studies to Measure Normal Physical Growth

The IOM report considered a spectrum of tools that can be used for assessment of ingredient safety, including preclinical in vivo (animal) and in vitro toxicity studies and clinical human studies. The committee recognized the importance of conducting a clinical study of a new ingredient under the intended conditions of use, i.e., in the context of human consumption of an infant formula product. Such a study also allows for the evaluation of the entire formula matrix, including interactions among formula components. IOM recommended that "bioavailability be specifically addressed in any evaluation of the safety of infant formulas" (Ref. 3 at 5). Thus, IOM's recommendations included the importance of assessing the bioavailability of an infant formula and its nutrients.

The IOM report states that "growth studies should remain the centerpiece of clinical testing of ingredients new to infant formulas" (Id. at 113). The IOM report concludes that "the inability of a formula to support growth represents a significant harm to infants and therefore growth is an essential endpoint for all safety assessments of an ingredient new to infant formulas" (Id. at 105). The IOM report recommends, however, that growth studies are not sufficient on their own to assess ingredients new to infant formulas. IOM provides a hierarchical study of major organ systems and developmental-behavioral outcomes (Id. at 98). The IOM report states that "growth deficits are likely to appear only secondary to effects on specific organs or tissues and may not appear for some time after nutritional insult" (Id. at 113).

While clinical studies that measure other aspects of the bioavailability of nutrients in an infant formula may prove valuable at a future time, FDA's current thinking is that it will not consider requiring additional measurements, under section 412 of the act, for the purpose of assessing the bioavailability of the formula and its nutrients, beyond those measures identified in the 1996 proposed rule. Certain measurements that IOM recommends, other than growth studies, involve invasive procedures and may raise ethical concerns.

FDA is interested in receiving comments, based on the IOM report or other scientific information, concerning its current thinking that protein and physical growth are sufficient at this time for assessing the bioavailability of nutrients in an infant formula.

2. Body Composition as Measure of Normal Physical Growth

FDA proposed growth measurements that include body weight, recumbent length, head circumference, and average daily weight increment (proposed § 106.97(a)(1)(i)(B)). The IOM report recommends that growth measurements include weight, recumbent length, head circumference, weight and length velocity, and body composition (Id. at 107). Thus, FDA did not include a measure of body composition that IOM recommended.

FDA tentatively concludes that a measure of body composition is not necessary to include as a measure of physical growth when a clinical study is used to evaluate the quality factor of physical growth. The IOM report recommends that measurement of normal physical growth include body composition and lists anthropometry (e.g., skinfold measurements), dual x-ray absorptiometry, and isotope dilution as the most feasible methods (Id. at 107). IOM states that body composition is a "more sensitive indicator of infant nutritional status than measures of size," although body composition

measurement methods can be expensive and frequently inaccurate (Id. at 108). FDA believes that, due to the expense and frequent inaccuracy of body composition measurement methods, and the adequacy of measures of body weight, recumbent length, head circumference, and data to calculate average daily weight increment for assessing an infant's growth when fed an infant formula, measurement of body composition is not warranted at this time. FDA is interested in receiving comments, based on the IOM report or other scientific information, concerning its current thinking that measures of body weight, recumbent length, head circumference, and data to calculate average daily weight increment are adequate for assessing the quality factor of normal physical growth.

3. Duration of Clinical Studies and Enrollment Age of Infants

The IOM report recommends that, ideally, growth studies should be conducted over the entire period for which infant formula is intended to be fed as the sole source of nutrition, i.e., up to 6 months (180 days), which is consistent with breastfeeding guidelines (Ref. 2 at 10 and 112–113). IOM further states that a 120-day growth study, proposed by FDA, does not allow for the determination of delayed effects or for understanding longer-term effects of early perturbations in growth. This recommendation is based on breastfeeding guidelines that recommend exclusive breastfeeding for infants for at least the first 4 months of age and preferably for the first 6 months of age (Id. at 112). However, the IOM report acknowledges that "there is no reason to think that an adverse effect of an ingredient new to formulas would be detected *only* between 4 and 6 months of age"[3] and notes that many infants

[3]IOM seems to inadvertently alternate between discussion of the study length in terms of duration (i.e., a 180-day study), versus the length in terms of the infant's age (i.e., the study should continue until the infant is 6 months of age). Because most studies will not

Continued

begin consuming foods other than formula between 4 and 6 months of age (Id. at 112). Consumption of foods other than infant formula has the potential to confound a growth study evaluating an infant formula.

Although FDA agrees that the first 6 months of age is the optimal time to measure infant growth, and would not discourage clinical studies for this time period, FDA believes it is not necessary to conduct a clinical study, for the purpose of evaluating physical growth as a quality factor, for the infants' entire first 6 months of age.

FDA proposed that a clinical study be no less than 4 months in duration, enrolling infants no more than 1 month old at the time of entry into the study. FDA received several comments on this issue, both in response to the 1996 proposed rule and in response to the 2003 proposed rule. None of the comments were in favor of a study duration requirement of 6 months. The comments FDA received favored a duration requirement ranging between 112 and 120 days, and recommended an enrollment requirement of between the age of 8 days and 1 month.

To better capture the maximum amount of time during the most rapid growth period for infants, FDA is considering whether to require a time period for clinical studies of a period of no less than 15 weeks that would commence at no more than 2 weeks of age. FDA believes 15 weeks provides a sufficient amount of time for assessing the physical growth of infants. Given this relatively short time period and the importance of a sufficient length of time for determining growth outcomes, FDA believes it is important to require that the study commence no later than 2 weeks of age. These changes would result in a clinical study extending through approximately the infant's first 4 months

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commence on the day of the infant's birth, it is important to distinguish between the two. FDA has attempted to do so in its explanation of its current thinking on this issue.

of age. A required study duration of no less than 15 weeks corresponds to the Iowa reference data recommendations regarding the duration of a clinical study. FDA requests comments on whether, in light of the IOM report's 180-day recommendation, FDA should consider requiring a study period of no less than the infant's first 180 days (6 months). Comments should include any available supporting data and information.

III. What Comments Will Be Considered?

Comments submitted in response to this proposed rule should focus solely on one or more of the following issues: (1) Whether FDA should require a microbiological standard for *E. sakazakii* for powdered infant formula of negative in 30 x 10 g samples; (2) whether FDA should not require microbiological standards for aerobic plate count, coliforms, fecal coliforms, *Listeria monocytogenes*, *Staphylococcus aureus*, and *Bacillus cereus*; (3) whether FDA should require measurements of healthy growth beyond the two proposed quality factors of normal physical growth (as measured by body weight, recumbent length, head circumference, and average daily weight increment) and protein quality; (4) whether FDA should require a measure for body composition as an indicator of normal physical growth, and if so, what measure, and (5) whether FDA should require the duration for a clinical study, if required, be no less than 15 weeks, and commence when infants are no older than 2 weeks of age. FDA requests comments on how, if we make the changes to the proposed rule outlined in this document, the costs and benefits would either be greater or less than estimated in the 1996 proposed rule (61 FR 36154 at 36202). We also request comment on the extent to which the description of industry practices in the Rome meeting report (Ref. 2) accurately describes the activities of all firms supplying infant formula in the United States. Data

supplied in response to these questions will be used to inform any rulemaking. FDA will not consider comments outside the scope of these issues.

Comments previously submitted to the Division of Dockets Management do not need to be resubmitted, because all comments submitted to the docket number, found in brackets in the heading of this document, will be considered in development of the final rule.

IV. How to Submit Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Docket Management between 9 a.m. and 4 p.m., Monday through Friday.

V. References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site addresses, but we are not responsible for subsequent changes to the Web sites after this document publishes in the **Federal Register**.)

1. The Food and Agriculture Organization of the United Nations and the World Health Organization, "*Enterobacter sakazakii* and Other Microorganisms in Powdered Infant Formula: Joint FAO/WHO Meeting 2–4 February 2004," available at *http://www.fao.org/documents/show_cdr.asp?url_file=/docrep/007/y5502e/y5502e00.htm* (last visited May 10, 2006).

2. The Food and Agriculture Organization of the United Nations and the World Health Organization, "*Enterobacter sakazakii* and *Salmonella* in Powdered Infant

Formula: Meeting Report, FAO Headquarters, Rome, Italy, 16–20 January 2006," available at *ftp://ftp.fao.org/ag/agn/jemra/e_sakakazii_salmonella.pdf* (last visited May 10, 2006).

3. Committee on the Evaluation of Ingredients New to Infant Formula, "Infant Formula: Evaluating the Safety of New Ingredients," National Institute of Medicine, March 1, 2004.

Dated: 7/24/06

July 24, 2006.

Jeffrey Shuren,
Assistant Commissioner for Policy.

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