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DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration

21 CFR Parts 106 and 107

[Docket No. 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 60 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 (61 FR 36154), revising its infant formula regulations in 21 CFR parts 106 and 107. The proposed rule would establish requirements for current good manufacturing practice (CGMP) and audits, establish requirements for quality factors, and amend its quality control procedures, notification, and records and reports requirements for infant formula. FDA is reopening the comment period to update comments and to receive any new information.

DATES: Submit written or electronic comments by *[insert date 60 days after date of publication in the Federal Register]*.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061,

Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>.

FOR FURTHER INFORMATION CONTACT: Shellee Anderson, Center for Food Safety and Applied Nutrition (HFS-800), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, 301-436-1491, or e-mail: Shellee.Anderson@cfsan.fda.gov.

SUPPLEMENTARY INFORMATION:

I. Reopening of Comment Period

In the **Federal Register** of July 9, 1996 (61 FR 36154), FDA proposed regulations (the 1996 proposal) to revise its infant formula regulations to establish requirements for quality factors and CGMP; to amend its 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 their shelf life, and that they be produced under strict microbiological controls; and to require that 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).

Interested persons were originally given until October 7, 1996, to comment on the 1996 proposal. However, at the request of a trade organization, the comment period was extended to December 6, 1996 (61 FR 49714, September 23, 1996).

FDA's Food Advisory Committee (FAC) met on April 4 and 5, 2002, to discuss general scientific principles related to quality factors for infant formula. The committee was also asked to discuss the scientific issues related to the generalization of findings from a clinical study using preterm infant formula consumed by preterm infants to a term infant formula intended for use by term infants. On November 18 and 19, 2002, the Infant Formula Subcommittee (IFS) of the FAC met to discuss the scientific issues and principles involved in assessing and evaluating whether a "new" infant formula supports normal physical growth in infants when consumed as a sole source of nutrition. The Contaminants and Natural Toxicants Subcommittee (CNTS) of the FAC met on March 18 and 19, 2003, to discuss the scientific issues and principles involved in assessing and evaluating *Enterobacter sakazakii* contamination in powdered infant formula, risk reduction strategies based on available data, and research questions and priorities. Information on these three meetings, including the agenda, questions asked, guest speakers, committee roster, briefing information, and transcripts of the meetings can be found at <http://www.fda.gov/ohrms/dockets/ac/cfsan02.htm>.

II. Request for Comments

Because of the length of time that has elapsed since publication of the 1996 proposal and the occurrence of the FAC, IFS, and CNTS meetings, FDA is interested in updating comments and receiving any new information before issuing a final rule. Accordingly, the agency is requesting comments on all issues in the proposed rule. Comments previously submitted to the Dockets Management Branch do not need to be resubmitted because all comments submitted to the docket number will be considered in any final rule to the

1996 proposal. Since the 1996 proposal was published, several issues within the scope of that proposal have come to the agency's attention and are set forth in this document for comment.

(Issue 1) In April 2001, an outbreak of *E. sakazakii* occurred in 10 infants in the neonatal intensive care unit of a hospital in Tennessee (Ref. 1). One of these infants died. The ill infants had consumed formula that was made from sterile water and a specific batch of powdered infant formula. Samples from both opened and unopened cans of the implicated brand of powdered infant formula were cultured. *E. sakazakii* was found in all samples from one particular batch of the product. Because of its concerns with *E. sakazakii*, FDA requests 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 prevent future outbreaks. The agency requests comment on what other changes, if any, in the proposed microbiological requirements would be appropriate to ensure the safety of powdered infant formula and to prevent outbreaks of illness. FDA also requests comment on whether powdered infant formula to be consumed by premature and newborn infants should meet stricter microbiological requirements than formula intended for older infants. The agency specifically requests comments on issues discussed at the CNTS meeting that are relevant to this rulemaking.

(Issue 2) On March 19, 2002, FDA issued a letter (Ref. 2) in response to a notice of a manufacturer's conclusion that *Bifidobacterium lactis* strain Bb12 and *Streptococcus thermophilus* strain Th4 are generally recognized as safe (GRAS) for their intended use as ingredients in milk based infant formula that is intended for consumption by infants 4 months and older, at levels not to

exceed CGMP. The agency has no questions about the manufacturer's conclusion at this time. In the 1996 proposal, FDA provided controls in proposed § 106.55 for powdered infant formula to prevent adulteration from microorganisms, including a proposed limit on the maximum allowable number of microorganisms in the aerobic plate count. The agency requests comment on what changes, if any, in the proposed microbiological requirements would be appropriate to provide for powdered infant formula and to ensure its safety if microorganisms are intentionally added to infant formulas. Would infant formula containing these added microorganisms exceed the maximum allowable number in the aerobic plate count? How can manufacturers ensure that a high aerobic plate count is due to the intentional addition of microorganisms and not contamination?

(Issue 3) The agency requests comments on which provisions of the proposed rule would require manufacturers to change their current activities. What new activities would manufacturers have to undertake to comply with the proposed regulations? What activities would manufacturers have to discontinue to comply with the proposed regulations? What are the costs of these changes? For example:

(Issue 3a) Proposed § 106.20(a) requires that buildings used in the manufacture of infant formula allot space for the separation of incompatible operations, such as the handling of raw materials, the manufacture of the product, and packaging and labeling operations. FDA requests comment on the types of control systems that manufacturers use to separate raw, in-process, and finished materials and the costs of making changes.

(Issue 3b) Proposed § 106.20(d) would require manufacturers to use air filtration systems, including prefilters and particulate matter air filters, on air

supplies to production areas where ingredients or infant formula are directly exposed to the atmosphere. FDA requests comment on the types and costs of air filtration systems used by infant formula manufacturers and the costs of making changes.

(Issue 4) One comment to the 1996 proposal stated that the validation section in proposed § 106.35 is so vague and the impact so enormous that implementing it would be counterproductive. In proposed § 106.35(a)(4) the agency proposed that, for purposes of the section, "validation" means establishing documented evidence that provides a high degree of assurance that a system will consistently produce a product meeting its predetermined specifications and quality characteristics. In proposed § 106.35(b)(1), FDA proposed that all automatic systems be designed, installed, tested, and maintained in a manner that will ensure that they are capable of performing their intended function. The agency proposed in proposed § 106.35(b)(4) that automatic systems be validated before their first use to manufacture commercial product. Proposed § 106.35(b)(5) states that the infant formula manufacturer shall ensure that any automatic system that is modified be validated after the modification and before use of the modified system to manufacture commercial product. FDA requests comments on the proposed validation requirements. The agency specifically requests comments on current validation activities of infant formula facilities and how often manufacturers validate their systems.

(Issue 5) Several provisions of the 1996 proposal (e.g., §§ 106.30(d)(1) and 106.35(b)(2)) would require that manufacturers calibrate instruments and controls. In these proposed provisions the agency specifies that calibration occur at routine intervals. FDA requests comments on how often and under

what conditions manufacturers now calibrate instruments and controls against a known standard and the adequacy of current procedures.

(Issue 6) FDA proposed to establish two quality factor measures for infant formula, protein quality and normal physical growth. Quality factors are those factors necessary to demonstrate that the infant formula, as prepared for market, provides nutrients in a form that is bioavailable and safe as shown by evidence that demonstrates that the formula supports healthy growth when fed as a sole source of nutrition. The agency requests comments on the appropriateness of these quality factors and any information on other quality factors that could be implemented to be consistent with current scientific knowledge as required under section 412(b)(1) of the act. FDA specifically requests comments on issues relevant to this rulemaking that were discussed at the two FAC meetings and on the following quality factor issues:

(Issue 6a) What requirements should the agency establish to determine when manufacturers must conduct clinical growth studies for a new or reformulated infant formula?

(Issue 6b) In proposed § 106.97, FDA would require that manufacturers compare their clinical study growth data with the National Center for Health Statistics (NCHS) growth charts. The IFS of the FAC considered other sources of reference data in addition to the NCHS and recommended the Iowa reference data as the most appropriate reference data for comparison because they are longitudinal, collected over the time period of interest for clinical studies of infant growth, and collected in a research setting. FDA requests comments on whether the Iowa reference data should be the standard for clinical study growth data rather than the NCHS growth charts.

(Issue 6c) In proposed § 106.97(a)(1)(i)(A), the agency would require that manufacturers conduct clinical studies that are no less than 4 months in duration, enrolling infants no more than 1 month old at time of entry into the study. The IFS of the FAC recommended that infants be enrolled by 14 days of age. FDA requests comments on the appropriate age for infants enrollment into clinical studies and on the duration of the studies.

(Issue 7) In proposed § 106.97(a)(1)(ii), the agency states provisions that it recommends manufacturers include in a clinical study protocol. Proposed § 106.97(a)(1)(ii)(C) discusses review and approval by an Institutional Review Board (IRB) in accordance with part 56 (21 CFR part 56), and the need for obtaining written informed consent from parents or legal representatives of the infants in accordance with part 50 (21 CFR part 50). Subsequent to the publication of the 1996 proposal, the agency issued an interim final rule entitled "Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products" (66 FR 20589, April 24, 2001), which amended parts 50 and 56 to include, within the scope of that rule, data and information about a clinical study of an infant formula when submitted as part of an infant formula notification under section 412(c) of the act. Thus, requirements related to IRB review and informed consent for such clinical studies are dealt with in that interim final rule, and therefore, reference to IRB review and informed consent will be removed from the 1996 proposal. With respect to the other clinical study protocol provisions in proposed § 106.97(a)(1)(ii), the agency intends to remove them from the proposed rule and develop a guidance document on what it recommends be included in a clinical study protocol for infant formula that is submitted as part of an infant formula notification under section 412(c) of the act.

III. How to Submit Comments

Interested persons may submit to the Dockets Management Branch (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments to <http://www.fda.gov/dockets/ecomments> 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 Docket Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

IV. References

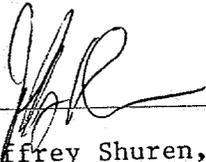
FDA has placed the following references on display in the Dockets Management Branch (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Centers for Disease Control and Prevention, "*Enterobacter sakazakii* Infections Associated With the Use of Powdered Infant Formula—Tennessee, 2001," 51(14):297, *Morbidity and Mortality Weekly Report*, April 12, 2002.

2. FDA, Agency response letter to GRAS notice number GRN 00049, March 19,

2002.

Dated: 4/15/03
April 15, 2003.



Jeffrey Shuren,
Assistant Commissioner for Policy.

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