

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