procedures that are part of the written plan.

Proposed § 106.6(c) specifies requirements for a manufacturer's handling of any point, step, or stage in its production process where control of the process is necessary to prevent adulteration of the formula. These in-process control points, steps, or stages may include retorting or other heating steps, cooling steps, points where specific sanitation procedures are needed, product formulation control steps, points where cross contamination may occur, and steps where employee and environmental hygiene are necessary to prevent adulteration of the product.

Proposed § 106.6(c)(1) requires that infant formula manufacturers establish standards or specifications to be met at such points, steps, or stages. These standards or specifications establish the boundaries of safety at the point, step, or stage. Such standards or specifications may include, for example, upper and lower limits for parameters such as temperature, time, pH, visual appearance, and moisture level as well as chemical, nutrient, and microbiological specifications for raw materials. These standards or specifications can be set based on published or unpublished studies, on regulatory levels established by FDA, or on consultation with experts in infant formula production. As discussed in more detail below, FDA is proposing (see proposed § 106.100(e)(3)(i)) that manufacturers make and retain a list of the standards and specifications that they establish under proposed § 106.6(c)(1) including documentation of the scientific basis for each standard or specification. Maintaining such a list will mean that these standards and specifications are readily available for comparison to the actual values obtained in monitoring (i.e., making a planned sequence of observations or measurements) the production and in-process control system.

Proposed § 106.6(c)(2) requires that infant formula manufacturers monitor the points, steps, or stages in their production process where control is necessary to prevent adulteration of the infant formula. Regular monitoring of these points is necessary to ensure that the product meets the standards and specifications set under proposed § 106.6(c)(1) and to ensure that any trend toward loss of control is quickly identified. Quick identification will mean that adjustments can be made to prevent a deviation from occurring, or, in the event that a deviation does occur, that effective corrective actions can be taken to remove adulterated product from the system.

For many standards or specifications, continuous monitoring is possible. For example, temperature and time for a scheduled thermal process can be recorded continuously on temperature-recording charts. When it is not possible to monitor a particular point, step, or stage on a continuous basis, monitoring intervals need to be reliable enough to permit the manufacturer to determine whether the production control point is under control.

Monitoring involves not only making observations at an appropriate frequency but also ensuring that the instruments and equipment, such as thermometers, temperature-recording devices, and computer software, that the manufacturer relies on to make its observations are accurate and reliable (see proposed § 106.30(d)).

Proposed § 106.6(c)(3) requires that infant formula manufacturers establish corrective action plans for use when a standard or specification established in accordance with proposed § 106.6(c)(1) is not met. FDA has tentatively concluded that this requirement is necessary because a manufacturer will often need to take corrective action quickly, and the best way to ensure that a corrective action is appropriate is to determine the action in advance. The corrective action plans should provide, for example, for the disposition of any infant formula or of any partially manufactured infant formula that was produced when a deviation was occurring.

Proposed § 106.6(c)(4) requires that infant formula manufacturers review the results of the monitoring required under proposed § 106.6(c)(2). This review will reveal whether the monitoring is actually being done and being done correctly, and whether standards and specifications are being met.

Proposed § 106.6(c)(4) further requires that infant formula manufacturers review, and evaluate the public health significance of, any deviations from standards or specifications established in accordance with proposed § 106.6(c)(1). This proposed requirement is necessary to ensure that products that may have been affected by a deviation do not enter commerce if they are likely to be unsafe. It also will ensure that the disruption of a manufacturer's business is minimized when a deviation does occur. For example, if review of monitoring records reveals that an ingredient premix does not contain the required nutrients at the required levels, the manufacturer can take steps to dispose of the premix before it is used in the manufacture of an infant formula. If the monitoring records are not reviewed, a product made with a deficient premix may be placed on the market, and a costly and embarrassing recall may be required.

Proposed § 106.6(c)(4) also requires that this review be conducted by an individual qualified by training and experience to conduct such reviews. This proposed requirement is necessary to ensure that the review is conducted by a person who understands the production and in-process control system, understands the significance of a processing deviation, and knows how to respond to a deviation. Such understanding and knowledge will ensure that the review is appropriately conducted, and that the response to any deviation is measured and appropriate.

Proposed § 106.6(c)(5) requires that infant formula manufacturers establish recordkeeping procedures, in accordance with proposed § 106.100(e)(3), that ensure that compliance with the requirements of proposed § 106.6(c) is documented. As discussed below in the description of the proposed revisions to subpart F of part 106, FDA has authority to require that these records be made and retained under section 412(b)(4)(A)(i) of the act. FDA is proposing to provide a complete description of all recordkeeping requirements in subpart F. When applicable, FDA is including cross-references to these recordkeeping requirements in the regulations in subparts B, C, and D. These records will allow manufacturers to discern trends or to pinpoint the onset of a problem if a standard or specification is not being met at a point where control is deemed necessary to prevent adulteration, or if a batch of infant formula is associated with an adverse event.

3. Controls to Prevent Adulteration by Workers

Proposed § 106.10(a) requires that there be sufficient personnel, qualified by training and experience, to perform all operations, including all required recordkeeping, in the manufacture, processing, packing, and holding of each infant formula and to supervise such operations to ensure that they are correctly and fully performed. Proposed § 106.10(a) is consistent with existing regulations concerning CGMP for foods (§ 110.10(c)) and drugs (§ 211.25). In this provision, FDA is proposing a general standard for determining how many employees are necessary, i.e., that there be enough to achieve, maintain, and document CGMP. However, FDA is leaving the determination of the actual number of employees necessary to the manufacturer's discretion.

Proposed § 106.10(a) also requires that such personnel be qualified by training and experience. Training is necessary to ensure that employees know how to correctly and fully perform the operations in question and to ensure that employees are competent to produce a safe and clean infant formula. The extent and frequency of training is left to the manufacturer's discretion.

Proposed § 106.10(b) requires that personnel working directly with infant formula, infant formula raw materials, infant formula packaging, or infant formula equipment or utensil contact surfaces practice good personal hygiene to protect the product against contamination. Proposed § 106.10(b) is consistent with existing regulations concerning CGMP for foods (§ 110.10(b)) and drugs (§ 211.28(a) and (b)). FDA has tentatively concluded that it is necessary that these employees practice good hygiene so that they will not transmit disease to others in the workforce, and so that they will not transmit filth or pathogenic microorganisms to the infant formula.

In addition, proposed § 106.10(b) enumerates the basic elements of good personal hygiene. Proposed § 106.10(b)(1) lists clean outer garments and protective apparel as one element. To be "clean," clothing must be free of filth or microorganisms that may contaminate the infant formula. Protective apparel, such as head, face, hand, and arm coverings, will help to ensure that the infant formula is protected from contaminants such as hair.

Proposed § 106.10(b)(2) states that good personal hygiene includes workers washing their hands thoroughly in a hand washing facility with soap and running water at a suitable temperature before starting work, after each absence from the work station, and at any other time when hands may become soiled or contaminated. Filth and pathogenic microorganisms can be brought into the processing environment on the employee's hands from outside areas, restrooms, contaminated raw materials, waste or waste receptacles, and other insanitary objects (Refs. 10, 11, and 12). FDA has tentatively concluded that requiring workers to practice good personal hygiene by washing their hands at the times specified will help to prevent the introduction of this type of contamination into infant formula.

Proposed § 106.10(c) requires that any person who reports that he or she has, or appears by medical examination or supervisory observation to have, an illness, open lesion, including boils, sores, or infected wounds, or any other source of microbial contamination that creates a reasonable possibility that the safety of the formula may be adversely affected, be excluded from direct contact with ingredients, containers, closures, in-process materials, equipment, utensils, and infant formula product until the condition is corrected or determined by competent medical personnel not to jeopardize the safety of the infant formula. Proposed § 106.10(c) is consistent with existing regulations concerning CGMP for foods (§ 110.10(a)) and drugs (§ 211.28(d)). Employees can transmit the organisms responsible for diseases, such as salmonellosis, shigellosis, and hepatitis, to the infant formula. Additionally, open sores, boils, or infected wounds present the potential for contamination of the infant formula with such pathogenic microorganisms as *Staphylococcus aureus* (Refs. 14 and 15). Thus, proposed § 106.10(c) will exclude employees who carry potential microbial contamination that may adversely affect the safety of the formula from direct contact with the infant formula and from direct contact with materials and surfaces that come in contact with the infant formula and thus will minimize the potential for employees to transmit microorganisms to the infant formula that may cause the infant formula to pose a health hazard to the infant.

4. Controls to Prevent Adulteration Caused by Facilities

Proposed § 106.20(a) requires that buildings used in the manufacture, processing, packing, or holding of infant formula be maintained in a clean and sanitary condition. This proposed requirement is necessary to prevent contamination of the infant formula. It is consistent with FDA's existing regulations concerning CGMP for foods (§§ 110.20(b) and 110.35(a)) and drugs (§ 211.42). Trash, litter, and waste must be disposed of to avoid creating conditions that attract and harbor potentially pathogenic microorganisms and attract and harbor pests, such as rodents or insects. Such pests can carry a variety of human disease agents, including microorganisms that are potentially pathogenic in infants, and introduce them into the manufacturing environment (Refs. 10 and 12). They are also sources of feces and hair that can contaminate infant formula.

Proposed § 106.20(a) also requires that buildings used in the manufacture of infant formula have space for the separation of incompatible operations, such as the handling of raw materials, the manufacture of the product, and packaging and labeling operations. If raw materials are not separated from the site of product manufacture, there is a significant possibility that they will be used in infant formula manufacture before they have been tested and found acceptable for use in infant formula. Therefore, FDA has tentatively concluded that the separation of incompatible operations is necessary to ensure that infant formula is manufactured in a manner designed to prevent adulteration. The proposed requirement that incompatible operations be separated is consistent with FDA's existing regulations concerning CGMP for foods (§ 110.20(b)(2)) and drugs (§ 211.42(c)) and is consistent with the recommendations made to FDA by the Infant Formula Council (Ref. 9).

Proposed § 106.20(b) requires separate holding areas to protect against mixups that could lead to contamination of infant formula. Failure to separate raw materials or in-process materials that have not been released, or that have been rejected but not disposed of, from those that have been released creates the potential for the use of ingredients that do not meet the applicable specifications and thereby can lead to the production of finished infant formula that is adulterated. Similar types of problems can develop if final product that has not been released, or that has been rejected but not disposed of, is not separated from final product that has been released. Proposed § 106.20(b) is consistent with FDA's existing regulations concerning CGMP for drugs (§ 211.42(c)).

Proposed § 106.20(c) defines a standard for adequate lighting and allows the manufacturer to exercise discretion in determining the precise level of lighting that is sufficient to meet that standard. Adequate lighting is important. Inadequate lighting may make it difficult to read a label or an instrument, and as a result incorrect ingredients may be used in infant formula production, or instruments may be read incorrectly, which increases the risk of producing an adulterated infant formula.

Proposed § 106.20(c) also requires that any lighting fixtures directly over or adjacent to exposed raw materials, in-process materials, or bulk (unpackaged) finished product be protected to prevent glass from contaminating the product in the event of breakage. Glass in an infant formula may be a safety hazard and would render the formula adulterated (Ref. 14). Proposed § 106.20(c) is consistent with FDA's existing regulations concerning CGMP's for food (§ 110.20(b)(5)) and drugs (§ 211.44).

FDA is proposing a requirement in § 106.20(d) for air filtration systems to improve air quality in production areas

and thus reduce the potential for contamination by air-borne sources (Ref. 15). This proposed requirement is consistent with FDA's existing regulations concerning CGMP for drugs (§ 211.46(c)).

Proposed new requirements in § 106.20(e) protect against the contamination of infant formula by pest control agents and cleaning agents. The agency recognizes that these agents are needed in infant formula facilities. However, because many of them are toxic, they must be handled and stored in a manner that prevents contamination of the infant formula. Proposed § 106.20(e) is consistent with FDA's existing regulations concerning CGMP for food (§ 110.35(b)(2)) and drugs (§ 211.56(c)).

Proposed § 106.20(f)(1) states that potable water used in the manufacturer of infant formula must meet the Environmental Protection Agency's (EPA's) Primary Drinking Water Regulations (40 CFR part 141) (with the one exception that the fluoride level be as low as possible, as discussed below). This proposed regulation is consistent with FDA's existing regulations concerning CGMP for drugs (§ 211.48(a)).

The Safe Drinking Water Act gives EPA the responsibility for establishing standards for public drinking water. Therefore, FDA is proposing to use EPA's standards for water used in the production of infant formulas. Application of these standards will ensure that the water used in infant formula is safe. The agency is proposing to require that water from both municipal sources and the firm's own wells meet these standards.

The safety and sanitary quality of water from public water systems is generally ensured through public water treatment, chlorination, or monitoring and control by local health authorities. Private sources of water, however, particularly surface waters or water from shallow wells, may be subject to microbiological, chemical, or radiological contamination attributable to the source itself or to surface contamination at the well head or intake. Private sources are also frequently untreated or minimally treated. Thus, under the proposed regulation, when a manufacturer uses a private source of water, it will need to take steps to ensure that the water is safe and sanitary. These steps may include ensuring that the well design has been approved by the local health authority, ensuring that the well meets coliform test standards, performing periodic inspections of the sanitary condition of the well head and source intake, and performing and monitoring appropriate water treatment procedures, including filtration, sedimentation, and chlorination. The type and frequency of controls exercised by the manufacturer will be based upon the type of source water and its historic safety and sanitary quality.

Proposed § 106.20(f)(1) makes one exception to the use of EPA standards for drinking water. On April 2, 1986, EPA issued a maximum contaminant level (MCL) for fluoride in drinking water of 4 milligrams per liter (mg/L) (51 FR 11396) and reaffirmed this level on December 29, 1993 (58 FR 68826). The National Academy of Sciences (NAS) recommends 0.1 to 0.5 mg/day as the safe and adequate intake for infants from 0 to 6 months of age. Mottling of teeth in children has been observed at 2 to 8 milligrams/kilogram (mg/kg) concentration of fluoride in diet and drinking water (Ref. 16). Thus, if 4 mg of fluoride/L of water was allowed in the water used in infant formula manufacture, infants consuming ready-to-feed infant formula could receive enough fluoride to adversely affect their teeth. Currently, no infant formulas are manufactured with fluoridated water (Ref. 17), so that the pediatrician or other health care provider is able to decide whether a fluoride supplement is appropriate for formula-fed infants, principally by considering whether the formula was diluted with fluoridated water (Ref. 18).

NAS has established a safe and adequate daily dietary intake of fluoride for infants (Ref. 19). The agency is considering proposing to revise the infant formula nutrient requirements in § 107.100 to include fluoride and other nutrients that NAS has determined are essential for infants. FDA will consider fluoride levels for infant formulas at that time. FDA has tentatively concluded that, until it has revised the levels of required nutrients, manufacturers should continue their practice of not using fluoridated water in the manufacture of infant formula.

Proposed § 106.20(f)(1) also requires that the water be supplied under continuous positive pressure in a plumbing system that is free of defects that could contaminate an infant formula. FDA has tentatively concluded that this requirement is necessary to ensure that all potable water coming into the plant is not adversely affected by the in-plant plumbing. Contaminated water can serve as a vehicle for contamination of infant formula, both when used as an ingredient in the infant formula and when allowed to enter the product indirectly, as can occur, for example, when water is used to cool the product after retorting. Thus, FDA tentatively concludes that it is appropriate to include this positive requirement in this regulation.

Proposed § 106.20(f)(2), which sets forth requirements for testing representative samples of potable water used in infant formula manufacturing, is necessary to provide assurance that the water used in infant formula manufacturing meets EPA's standards. Proposed § 106.20(f)(3) requires that manufacturers conduct these tests with appropriate frequency. The regulation allows manufacturers some discretion in determining the testing frequency necessary to ensure that EPA standards are met, but it requires a minimum frequency of testing for certain contaminants (i.e., chemical contaminants, radiological contaminants, and bacteriological contaminants). FDA is basing these proposed minimum frequencies on those adopted by EPA for primary drinking water. This frequency of testing is consistent with FDA's own regulations concerning processing and bottling of bottled drinking water (§ 129.35(a)(3)).

Proposed § 106.20(f)(4) requires that manufacturers make and retain records of the frequency and the results of the testing that they do on the water used in the production of infant formula. These records will document that the manufacturer is complying with the potable water testing requirements of § 106.20(f)(2) and (f)(3), and that the water complies with EPA standards. They will identify any trend toward loss of compliance with these standards, so that the manufacturer can take corrective actions before the water becomes inappropriate for use in infant formula. As discussed below in the description of the proposed revisions to subpart F, FDA has authority to require the creation and retention of these records under section 412(b)(4)(A)(i) of the act.

In proposed § 106.20(g), FDA sets out requirements regarding piping systems to prevent a source of contamination (i.e., waste water) from coming in contact with the infant formula. Cross connections could allow back siphonage into a potable system from a nonpotable system under negative pressure conditions and thus could result in the chemical or microbiological contamination of the potable water system (Ref. 20). Proposed § 106.20(g) is consistent with FDA's regulations concerning CGMP for food (§ 110.37(b)(5)) and drugs (§ 211.48(b)).

Proposed § 106.20(h) requires that steam that comes in direct contact with infant formula be safe and free of rust

and other particulate matter that could contaminate the formula. Steam comes in direct contact with infant formula when the steam is injected into the head space of a can of infant formula to create a vacuum. Thus, this proposed requirement is necessary to ensure that the steam does not adulterate the infant formula.

Proposed § 106.20(h) also requires that boiler water additives in the steam meet safety standards set forth in FDA regulations at 21 CFR 173.310 which lists boiler water additives that may be safely used in the preparation of steam that will contact food and the conditions for the safe use of those boiler water additives. This proposed requirement is necessary because boiler water additives dissolve in water and can be carried over as a residue in the steam. A proposed requirement that boiler water additives in the steam comply with § 173.310 will ensure that any residue is safe to come in contact with the infant formula.

Proposed § 106.20(i) requires that each infant formula manufacturing site provide its employees with readily accessible toilet and hand washing facilities. This proposed requirement is consistent with good sanitary practice common to all food-processing facilities and is consistent with FDA's CGMP regulations for foods (§ 110.37(d) and (e)) and drugs (§ 211.52). The requirement is also a necessary adjunct to the requirement in proposed § 106.10(b)(2) that employees wash their hands before starting work, after each absence from the work station, and at any other time when the hands may become soiled or contaminated. Hand-washing facilities are not likely to be used in an appropriate manner by employees if the facilities are not conveniently located.

Proposed § 106.20(i) also requires that these facilities be equipped with hot and cold water, ordinary soap or detergent, and single-service towels to ensure that microbiological contamination does not occur through the repeated use of the same towel by several individuals.

In addition, proposed § 106.20(i) requires that toilet facilities be maintained in good repair and in a sanitary condition at all times, and that these facilities provide for proper disposal of sewage, so that the processing environment is protected against pathogenic microorganisms shed in fecal material. Restroom floors and the grounds around the processing facility can become contaminated with pathogens if fecal material is not removed by an adequate sewage system. Foot traffic over the affected areas can introduce pathogens into the processing room and cause product contamination. Insanitary toilet facilities can also increase the potential for contamination of employees' hands and, ultimately, of the product itself (Refs. 10 and 11). Proposed § 106.20(i) further protects against potential microbiological contamination by setting forth requirements for the positioning of toilet facility doors.

5. Controls to Prevent Adulteration Caused by Equipment or Utensils

Equipment used in infant formula manufacture, packaging, or holding that is of an inappropriate design or an inadequate size, or that is installed improperly, can result in a variety of problems. For example, a mixer for the blending of powdered ingredients will not properly perform its function if the blade is too small relative to the size of the mixer, or if the mixer blade or auger is not properly positioned in the inside of the mixer. Such a mixer may produce infant formula that is not uniform in composition throughout a batch and that is, consequently, adulterated because the required nutrients are not provided at the required levels throughout the batch.

Installing equipment in a manner that will facilitate its cleaning and maintenance is also important in preventing adulteration. Equipment that is not properly cleaned can be the source of contaminants that adulterate the infant formula. Equipment that is not properly maintained can result in a variety of problems. For example, improper maintenance of equipment such as a mixer may result in inadequate compositional uniformity in a batch of formula. Improper maintenance of equipment used to measure a parameter such as temperature may result in the processing of the infant formula at a temperature that can adversely affect the product. In either case, the product would be adulterated. Design and installation of equipment also needs to be checked when the equipment is modified or repaired to ensure that the equipment is still designed and installed to function as intended as part of the manufacturing process. Thus, proposed § 106.30(a) requires that equipment be appropriately designed and installed. This proposed requirement is consistent with FDA's CGMP regulations for foods (§ 110.40(a)) and drugs (§ 211.63).

If a food-contact surface is constructed of toxic material, the product may be directly contaminated with that material (Ref. 11). Therefore, FDA is proposing to require in § 106.30(b) that equipment and utensils be made of materials that are not reactive or absorptive, so that the equipment and utensil materials do not contaminate the infant formula and cause it to be adulterated. Proposed § 106.30(b) also requires that such equipment and utensils be designed to be easily cleanable because they can be vehicles for microbial contamination of both raw and finished products. Utensils, equipment, and other food-contact surfaces that are made of corrosive material, or that contain breaks, pits, cuts, or grooves, are difficult to clean because the pores and crevices shield the microorganisms from the action of cleaning and sanitizing agents (Ref. 21). In addition proposed § 106.30(b) requires that equipment and utensils be designed to withstand the environment in which they are used. This requirement will ensure that equipment and utensils are constructed of materials that will not corrode or undergo other types of chemical or physical degeneration resulting from their use in infant formula production. Degeneration of the equipment and utensils may introduce contaminants into the formula and thereby lead to adulteration. Surfaces that are not adequately cleaned and sanitized can be a source of filth, an attractant for vermin, and a reservoir for microorganisms.

Proposed § 106.30(b) requires regular, effective cleaning and sanitizing of all food-contact surfaces to minimize the probability of contamination of the infant formula (Ref. 21) and prescribes requirements for effective sanitizing agents. An effective sanitizing agent is one that has a good bactericidal effect on the types of microorganisms normally present in the plant environment and that is safe, stable, and convenient for use (Ref. 22). Sanitizing agents are indirect food additives and must be used in accordance with 21 CFR 178.1010, which prescribes their conditions of safe use. Examples of sanitizing agents that comply with § 178.1010 include hypochlorites, iodophors, and quaternary ammonium compounds. However, sanitizers can achieve their intended effect only if they are applied to a surface that has been thoroughly cleaned, and if they are applied at a proper concentration (Ref. 22).

Thus, it is important that effective cleaning compounds be used. An effective cleaning compound is one that will lower the surface tension of water so that spills can be lifted and flushed away (Ref. 23). Ordinary soap has a limited ability to solubilize fats, oils, and proteins, and inorganic alkaline

detergents can dissolve food solids such as fats and proteins, but mineral deposits will frequently require the use of acid cleaners (Ref. 23).

In order to ensure that infant formula is not contaminated with unsafe substances that are a part of the manufacturing process, FDA is proposing requirements in § 106.30(c) regarding substances necessary for the operation of equipment, such as lubricants or coolants.

Proposed § 106.30(d)(1) sets forth requirements for maintaining the accuracy of instruments, since an instrument that is not easily read, or that is not properly calibrated, may not provide accurate measurements. If an instrument is not properly maintained, it may not be reliable over time, and the readings obtained from it may lead to adulteration of the infant formula during processing. This proposed regulation also requires that such instruments be sufficient in number for their intended use. For example, if the temperature of a large piece of equipment needs to be monitored, several temperature-indicating devices may be needed to accurately monitor the temperature in all parts of the equipment. Also, instruments and controls must be tested for accuracy (i.e., calibrated) against a known reference standard before first use and at routine intervals thereafter, as specified in writing by the manufacturer of the instrument or control, or as otherwise deemed necessary to ensure the accuracy of the instrument. FDA has tentatively concluded that this requirement is necessary because equipment used to manufacture infant formula must operate properly to ensure production of a safe, uniform product with a consistent nutrient content throughout a lot or a batch.

The accuracy of an instrument is the degree to which it produces a correct result. The instruments used to measure parameters such as temperature or pressure at points where control is deemed necessary to prevent adulteration must reflect the true measurement so that, for example, a manufacturer can have confidence that when a thermometer indicates that the temperature is 240 °F, the temperature really is 240 °F. FDA's experience is that calibration of the instrument using a reference standard is the most reliable method to ensure accuracy. FDA is proposing to require that this test for accuracy be done before first use to provide assurance that the instruments and controls will perform as intended and at routine intervals afterward to ensure that the instruments and controls continue to perform as intended.

Reliability is the instrument's accuracy over time. The reliability of the instrument will determine the length of time that it can be used before it begins to lose accuracy. The manufacturer of the instrument is in the best position to establish how frequently recalibration is needed because that manufacturer is responsible for putting together the technology by which the instrument operates. However, if the infant formula manufacturer's experience with the instrument demonstrates that the instrument needs to be calibrated more frequently than the instrument manufacturer suggests, FDA has tentatively concluded that the infant formula manufacturer must act on its own experience with the instrument and calibrate it as often as necessary to ensure the accuracy of the instrument.

Proposed § 106.30(d)(1) further requires that the known reference standard be certified for accuracy at routine intervals specified in writing by the manufacturer of the instrument, or as otherwise deemed necessary. Known reference standard devices are accompanied by certificates of accuracy, but these certificates do not preclude the possibility that these instruments will go out of calibration. Just as a calibration routine needs to be established for the process instrumentation, a recertification of the known reference standard needs to be established in accordance with the equipment manufacturer's recommendations. For example, the length of time that a certified thermometer can be considered reliable will depend on the materials used in its manufacture, the degree of control exercised in its manufacture, and its use, as would be the case for the indicating thermometer used in the production line. The accuracy of a calibrated thermometer is only going to be as good as the accuracy of the known reference standard that is used during its calibration.

Proposed § 106.30(d)(1) also requires that manufacturers make and retain records of accuracy checks in accordance with the provisions of proposed § 106.100(f)(2). As discussed below in the description of the proposed revisions to subpart F of part 106, FDA has authority to require these records under section 412(b)(4)(A)(i) of the act. These records will enable the manufacturer to establish the historical performance of the instrument to determine whether the calibration schedule is sufficient to ensure the accuracy of the instrument and will provide information on when and how the instruments were calibrated to assist the manufacturer in identifying the cause of a problem that may arise with a batch of infant formula.

Proposed § 106.30(d)(2) requires that instruments and controls that cannot be adjusted to agree with the reference standard be repaired or replaced. FDA is proposing this requirement because an instrument or control cannot be trusted for use in infant formula production if it cannot be adjusted to agree with the reference standard. Adjustments made to reach agreement with a known accurate or reference standard must also be done in accordance with any adjustment range limitations specified by the vender of the instrument.

Proposed § 106.30(d)(3) provides that if calibration of an instrument (testing for accuracy against a known reference standard) shows that a specification or standard has not been met at a point where control is deemed necessary to prevent adulteration, a written evaluation must be made of all affected product and of any actions that need to be taken. FDA has tentatively concluded that this written evaluation is necessary because if an instrument has been giving inaccurate readings, all infant formula produced subject to such inaccuracies must be identified and evaluated for the possibility that the inaccuracies resulted in the production of adulterated formula. If the manufacturer determines that adulterated formula has been produced, the firm must decide what actions, if any, need to be taken to prevent such formula from reaching infants.

FDA is also requiring that this written evaluation needs to be maintained in the firm's records. FDA tentatively concludes that this record is necessary to demonstrate that the firm has complied with CGMP. As discussed below in the description of the proposed revisions to subpart F of part 106, FDA has authority to require that these records be retained under section 412(b)(4)(A)(i) of the act.

Proposed § 106.30(e)(1) requires that the temperature in cold storage compartments used to store raw materials, in-process materials, or final product, as well as the temperature of thermal processing equipment used at points where temperature control is necessary to prevent adulteration, be monitored with such frequency as is necessary to ensure that temperature control is maintained. The frequency of the monitoring is left to the manufacturer to determine. Growth of microorganisms can occur and cause spoilage if materials that should be kept in cold storage compartments are not maintained at the proper temperature. Infant formula may also be adulterated if thermal processing equipment is not