operated at the proper temperature, and the final liquid infant formula product is not commercially sterile. Therefore, FDA tentatively concludes that their requirement is appropriate.

In addition, FDA is proposing that a temperature of 40 °F (4.4 °C) is appropriate in cold storage compartments to minimize the growth of pathogens (Ref. 24) and the deterioration of liquid ingredients, nutrients, and the formulated product before canning (proposed § 106.30(e)(2)).

Proposed § 106.30(e)(3)(i) requires that cold storage compartments and thermal processing equipment be equipped with easily readable, accurate temperature-indicating devices. These devices are necessary to ensure that the manufacturer can monitor the temperatures where materials are stored or where product is processed. Proposed § 106.30(e)(3)(ii) requires that thermal processing equipment be equipped with temperature-recording devices that reflect the true temperature on a continuing basis, so that the manufacturer will be able to determine whether the product was thermally processed at a minimum temperature for an appropriate period of time. Two factors, temperature and time, are relevant in ensuring that thermal processing is conducted in a manner that will produce commercially sterile infant formula after retorting. Thus, recording the temperature that is maintained during the time period used will show whether the thermal process is conducted properly.

Proposed § 106.30(e)(3)(ii) also requires that cold storage compartments be equipped with either a temperature-recording device that will reflect the true temperature within the compartment on a continuing basis, or a high-temperature alarm or a maximum-indicating thermometer that has been verified to function properly. These temperature records will show whether the materials were stored at an appropriate temperature to minimize the growth of pathogens and the deterioration of ingredients and formulated product. If the manufacturer does not wish to equip cold storage compartments with such temperature-recording devices, FDA is proposing to require that it maintain a temperature log in which the temperature in the compartment is noted with such frequency as is necessary to achieve control. The agency is leaving it to the manufacturer's discretion to determine what frequency of temperature notation is necessary to achieve control.

The agency has tentatively concluded that it is not necessary for the manufacturer to record the temperature of the cold storage compartment on a continuous basis as long as the manufacturer can determine that the temperature of the cold storage compartment has gone above 40 °F. A high-temperature alarm set to go off when the cold storage compartment goes above 40 °F will allow the manufacturer to make this determination. Likewise, a maximum-indicating thermometer will remain at the highest temperature that it ever reaches. If the maximum indicating thermometer indicates a temperature above 40 °F, the infant formula manufacturer must assume that the temperature has been above 40 °F since the last check of the thermometer. Thus, FDA has tentatively concluded that either a high-temperature alarm or a maximum-indicating thermometer are acceptable alternatives for determining whether the cold storage compartment has gone above 40 °F.

In some cases, the actual location of the sensors may be an important factor in ensuring the accurate representation of temperature. For example, one sensor located at the end of a large piece of thermal processing equipment may not accurately represent the temperature in the whole piece of equipment. In addition, these temperature devices must often be read under less than ideal plant conditions, so they should be installed in a location that facilitates easy reading. Temperature-recording devices can be easily jarred and rendered inaccurate. They can be recalibrated against a reference temperature-indicating device (e.g., a thermometer) quite easily, however. Manufacturers should do so at least at the beginning and end of each production day in order to determine whether the instrument was accurate throughout the day's production. For thermal processing equipment used to produce commercially sterile liquid infant formula, the mandatory and recommended procedures of 21 CFR part 113 apply.

FDA is also proposing that manufacturers make and retain records, in accordance with the provisions of proposed § 106.100(f)(3), of the temperatures indicated or recorded by these devices (see § 106.30(e)(3)). 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. They are needed to show that the thermal processing equipment or cold storage compartments are being maintained at the correct temperatures to prevent adulteration of the product. They also will enable the manufacturer to identify trends in temperature fluctuations that can signal the need to perform nonscheduled maintenance.

Proposed § 106.30(e)(4) requires that for thermal processing, the temperature-recording device not read higher than the calibrated temperature-indicating device because it is important to ensure that the infant formula is processed at a minimum temperature for a continual period of time. A temperature-recording device reading higher than the reference temperature-indicating device for thermal processing equipment would show that the product had been processed at a temperature higher than the true processing temperature. Because thermal processing is used to destroy microorganisms, a temperature-recording device reading higher than the true processing temperature may mean that the product has not been processed at a temperature that is high enough to destroy all microorganisms.

For cold storage compartments, the temperature-recording device must not read lower than the temperature-indicating device because when raw materials, in-process materials, or finished product must be stored at a cold temperature, it is important to ensure that the infant formula was not exposed to a temperature above the maximum temperature. A temperature-recording device reading lower than the reference temperature-indicating device for cold storage equipment would show the materials in the compartment as having been held at a lower temperature than the true temperature. Because cold storage is used to prevent microbiological growth, a temperature-recording device reading lower than the reference temperature-indicating device would mean that the material was actually being stored at a higher temperature than the recorded temperature, and that, as a result, microbial growth may have occurred.

Proposed § 106.30(f) requires that all equipment and utensils used in the manufacture of infant formula be cleaned, sanitized, and maintained at regular intervals to prevent adulteration of the infant formula. Any equipment or utensil that is not cleaned and maintained properly can be a source of contamination. FDA is therefore proposing to require that cleaning, sanitizing, and maintaining be done at regular intervals. The details of sanitation procedures e.g., equipment cleaning, can differ from plant to plant depending upon the type of operation and other conditions. In one plant, it may be necessary to disassemble all or part of the equipment to clean it. In other plants, breaking down the

equipment may not be necessary. Likewise, different cleaning compounds may be needed from one plant to another to solve specialized problems such as buildups of mineral deposits. Each manufacturer should study its own plant and develop a procedure that is tailored to that plant's needs and circumstances.

FDA considers that cleaning, sanitizing, and maintaining equipment and utensils is so important for ensuring that adulterated infant formula is not produced that it is proposing to require that the cleaning, sanitizing, and maintenance be checked for satisfactory completion by an individual qualified to conduct such a review. Such an individual will understand the importance of ensuring that cleaning, sanitizing, and maintenance is properly done, so that equipment and utensils do not contribute to the adulteration of the infant formula. Also, the agency has tentatively concluded that this requirement will ensure that there is accountability for proper performance of this function.

In addition, proposed § 106.30(f) requires that manufacturers make and retain records on equipment cleaning, sanitizing, and maintenance in accordance with proposed § 106.100(f)(4). As discussed below in the description of the proposed revisions to subpart F, FDA has authority to require these records under section 412(b)(4)(A)(i) of the act. These records will document when the cleaning, sanitizing, and maintenance of equipment occurs and will allow the manufacturer to trace all formula that may be affected if cleaning, sanitizing, or maintenance is not properly performed.

In order to ensure that compressed air or other gases will not contaminate the infant formula with unlawful indirect food additives or other chemical, physical, or microbiological contaminants, FDA is proposing to require in § 106.30(g) that they be appropriately treated. Air or other gases that are not properly treated and filtered, or air that is not of the proper purity, can introduce contaminants into the infant formula that may render it adulterated. Also, compressed gases can be contaminated with oil from the compressor or with filth or microbiological contaminants from the compression, storage, or distribution equipment. Filtration at the air intake and after compression, storage, and distribution is an effective means of reducing the risk that such contaminants will enter the gases and, thereby, the food. Therefore, FDA is also proposing in § 106.30(g) to require the use of a filter when compressed gases are used at product filling machines to replace air removed from the headspace of containers. The filter will prevent contaminants from entering the infant formula during that operation (Ref. 25).

6. Controls to Prevent Adulteration Due to Automatic (Mechanical or Electronic) Equipment

Manufacturers of infant formula are increasingly relying on automatic equipment (including mechanical and electronic equipment) in production and quality control. In some cases, manufacturers are replacing manually initiated processing procedures with automated process control systems to ensure proper formulation (addition of ingredients and premixes), mixing, or processing of an infant formula or to test a batch of infant formula. Such automated process control systems frequently consist of a computer or system of computers that controls many or all stages of production, in-process sampling, and testing. In other cases, manufacturers are relying on programmable equipment (such as an autoanalyzer) to perform a critical function, such as testing a batch of infant formula to ensure that the batch meets the nutrient requirements of the act. In all cases, it is important that such systems and equipment function as expected to ensure that the infant formula contains the required nutrients at the required levels and is manufactured according to the CGMP and quality control procedures prescribed under section 412(b)(2) of the act and therefore is not adulterated under section 412(a)(1) or (a)(3) of the act.

FDA is proposing to define "hardware," "software," "system," and "validation" in § 106.35 because the use of these terms will simplify the language of the proposed regulations and will clarify which sections of the proposed regulations apply to hardware only, to software only, or to systems consisting of both hardware and software.

The definition of "hardware" in proposed § 106.35(a)(1) is based on common usage of the term and makes clear that the regulations in proposed § 106.35 apply to all automatic equipment, whether the equipment is mechanical or electronic in nature. Proposed § 106.35(a)(1) also makes clear that electronic equipment includes, but is not limited to, computers. This definition of "hardware" distinguishes those elements of equipment that have a physical form from the elements considered to be intellectual property that may be encoded on a physical element such as a diskette, tape, or microprocessing chip.

Software may be developed by an infant formula manufacturer, by a manufacturer of equipment purchased by the infant formula manufacturer, or by a third party vendor (such as the vendor of a computer operating system). The definition of "software" in proposed § 106.35(a)(2) derives from the ISO International Guideline ISO-9000-3[1] (Ref. 26) and the Institute for Electrical and Electronics Engineers, Inc. (IEEE) Standard 610-12-1990[2] (Ref. 27) and is consistent with the definition of software in FDA's "Glossary of Computerized Systems and Software Development Terminology (Ref. 28). FDA is proposing to incorporate this definition into the agency's infant formula regulations because the definition is derived from internationally accepted definitions, includes documentation, applies to the operation of all types of hardware (rather than the narrowly defined "data processing system" or "computer system" included in the definitions from the ISO and IEEE, respectively), and is consistent with current FDA terminology. Software documentation consists of the instructions on how to use the software. FDA has tentatively concluded that such instructions need to be included in the definition of "software" to ensure the proper operation of the software.

The definition of "system" in proposed § 106.35(a)(3) derives from the IEEE Standard 610.12-1990 (Ref. 27). FDA is proposing to incorporate this definition because many of the requirements in proposed § 106.35 cannot be related to software or hardware alone but rather to systems in which software is used in conjunction with hardware. For example, testing software under simulated conditions of use may be beneficial during the early and middle stages of software development, but validation of the software must be performed in conjunction with the relevant hardware in the operational environment it is

[1] ISO is a world-wide federation of national standards bodies that set quality assurance guidelines for products that will enter international commerce. The ISO defines software as an "intellectual creation comprising the programs, procedures, rules and any associated documentation pertaining to the operation of a data processing system" (Ref. 26).

[2] IEEE is a trade organization comprised of several societies. IEEE standards are developed within the technical committees of the IEEE societies and represent a consensus opinion of experts from within IEEE as well as experts who are not members of IEEE. IEEE defines software as "computer programs, procedures, and possibly associated documentation and data pertaining to the operation of a computer system" (Ref. 27).

intended to be used in. Therefore in proposed § 106.35(b)(4), FDA is proposing that all systems be validated "before their first use to manufacture commercial product."

Proposed § 106.35(a)(4) defines "validation" as 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. It is important that a process control system comply with specified requirements each time it operates. The proposed definition is derived from the ISO International Guideline ISO–9000–3, (which defines "validation" as "the process of evaluating software to ensure compliance with specified requirements" (Ref. 26)); the IEEE Standard 610.12–1990, which (defines it as "the process of evaluating a system or component during or at the end of the development process to determine whether it satisfies specified requirements" (Ref. 27)); and FDA's "Glossary of Computerized System and Software Development Terminology," which defines it as "establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics" (Ref. 28). FDA is proposing to incorporate these definitions into its regulations because they are applicable to the types of systems used in infant formula manufacture, are derived from internationally accepted definitions, are consistent with existing FDA terminology, make clear that the process of evaluation includes the complete system (i.e., the hardware used in conjunction with the software), and include the concept of consistency.

Proposed § 106.35(b)(1) sets forth requirements for designing, installing, testing, and maintaining all systems so that they function as intended. Some systems may work properly only within a narrow range of environmental conditions, such as temperature and humidity, and some might be particularly sensitive to electromagnetic interference. The actual conditions of use of a system should be considered as early as possible in its design and development. Systems need to be installed in a manner that takes into account the inherent limitations of the system, tested under conditions that reflect actual conditions of use, and properly maintained to ensure that they continue to function as expected during their lifetime.

Proposed § 106.35(b)(2) requires that the manufacturer ensure that all hardware is routinely calibrated, inspected, and checked according to written procedures. FDA has tentatively concluded that this provision is necessary to ensure that any infant formula manufactured under the control of automatic equipment meets the requirements of the act and is manufactured in a manner designed to prevent adulteration. For example, a batch of infant formula may lack the required levels of nutrients if equipment used for the automatic dispensing of a nutrient premix is out of calibration or has a clogged delivery line. The routine calibration, inspection, and checking of hardware will ensure that it continues to perform as intended, and that its operation will not result in a process that deviates from established specifications. The establishment of written procedures for the calibration, inspection, and checking of hardware will ensure that these procedures are performed consistently and in an appropriate way.

The incorporation of software into the operation of automatic equipment has not only increased the complexity of such equipment but also has resulted in a process that may operate differently for each execution because a software-based control system can be configured at will by the operator or by the system itself. Therefore, proposed § 106.35(b)(3), (b)(4), and (b)(5) require that manufacturers exercise appropriate controls over systems and, in particular, over the software used in the systems.

Proposed § 106.35(b)(3) prescribes procedures for ensuring that systems are checked for input and output errors resulting from faulty data entry, faulty programming, or equipment malfunction. Such errors can result in serious production or quality control errors leading to a contaminated or adulterated infant formula. For example, a faulty position sensor on a downstream valve that improperly indicates that it is closed may result in a post-sterilization contamination. An improperly installed (or empty) ink cartridge in a color printer or multi-pen recorder may cause portions of a record to not be printed. FDA has tentatively concluded that the regulation is necessary to ensure that the infant formula produced or analyzed using the system is not adulterated. However, proposed § 106.35(b)(3) also provides that the degree and frequency of input/output checks are to be based on the complexity and reliability of the system and the level of risk associated with the safe operation of the system.

Proposed § 106.35(b)(4) requires that manufacturers ensure that all systems are validated before their first use to manufacture commercial product. FDA has tentatively concluded that it is necessary that software programs that are used in a process control system to monitor and control established points deemed necessary to prevent adulteration (such as the speed of a pump, temperature of a heat exchanger, addition of vital nutrients, and air overpressure in an aseptic storage tank) be validated to ensure that use of the process control system will produce compliance with the specifications or standards at each control point. For example, if a continuous flow process is designed to heat an in-process batch of infant formula in a plate-to-plate heat exchanger to a specification of 271 °F, as indicated by the temperature at the end of the hold tube, and the system is mistakenly programmed to divert the product to the raw (unsterilized) surge tank only if the temperature drops below 261 °F, an in-process batch of infant formula heated to 261 °F would not be diverted to the raw surge tank but rather would be handled by the computer as if it were adequately processed. Such an underprocessed batch of infant formula would likely pose a foodborne biological hazard. Thus, FDA has tentatively concluded that the validation required under proposed § 106.35(b)(4) is necessary to ensure that infant formula that is produced or analyzed using the system is not adulterated.

The validation of software ordinarily includes the following elements: Requirements development, design, coding, debugging, testing (with the hardware), and maintenance (Refs. 29, 30, and 31). Software validation also includes a review for correctness of the software documentation to ensure that the instructions prompt the input of the proper commands or data by the user. However, depending on the nature of the software and the hardware that it controls, some or all of these aspects of the validation process may be done by the infant formula manufacturer, by the manufacturer of equipment that is purchased by the infant formula manufacturer, or by a third party vendor.

Proposed § 106.35(b)(4) leaves the identity of the person that does the validation to the discretion of the infant formula manufacturer but makes clear that the infant formula manufacturer is responsible for ensuring that the system is validated. The proposal does not stipulate any standards or specifications for the validation process because the extent of the validation necessary is

related to the level of risk that each component of the system presents.

More emphasis should be placed on validating portions of the system that represent major risk than on those that confer moderate or minor risk. A major risk is associated with systems that control or monitor a point where such control or monitoring is deemed necessary to prevent adulteration of the infant formula; for example, systems that control or monitor nutrient addition or processing temperature present a major risk. A moderate risk is associated with systems that influence, but that do not control or monitor, a point where control or monitoring is deemed necessary to prevent adulteration of the infant formula. For example, the speed of computer processing presents a moderate risk if software that is designed to be used on a high-speed computer is used on a slower computer. A minor risk is associated with systems that do not involve a point where control or monitoring is deemed necessary to prevent adulteration. For example, systems that control pallet stacking or product conveying present a low risk.

Proposed § 106.35(b)(5) requires that any system that is modified be revalidated after any modification and before use of the modified system to manufacture commercial product. FDA has tentatively concluded that revalidation is necessary to ensure that no errors are introduced into the system during the modification and to ensure that a modification in one aspect of a process control system does not, unknowingly but adversely, affect other aspects of the process control system, particularly those operations that follow the modified aspect of the system.

Under § 106.35(b)(5), FDA is also proposing that a specific individual (or group of individuals) is designated to modify software to prevent the indiscriminate modification of software and to ensure that all modifications are made consistently. The designated individual may be employed by the infant formula manufacturer, the manufacturer of equipment purchased by the infant formula manufacturer, or by a third party. The regulation states, however, that the infant formula manufacturer is responsible for ensuring that modified software is retested or revalidated regardless of who does the modification.

Proposed § 106.35(c)requires that infant formula manufacturers make and retain records concerning automatic (mechanical or electronic) equipment. FDA is proposing this requirement under the authority of section 412(b)(4)(A)(i) of the act, which requires the retention of all records necessary to demonstrate compliance with the CGMP and quality control procedures prescribed under section 412(b)(2) of the act, including the results of all testing required under section 412(b)(2)(B) of the act. These records will allow manufacturers to readily determine whether this crucial equipment is being appropriately operated and maintained. They will allow manufacturers to troubleshoot and to operate these systems with a minimum of downtime when problems occur because the records will include a copy of all software used and a backup file of data entered into the computer or related system which can be used to reload the system. The records will also provide information that the manufacturer can use in trying to determine why a problem with the system is occurring or why the system is not producing an infant formula that complies with the manufacturer's specifications for the product.

7. Controls to Prevent Adulteration Caused by Ingredients, Containers, and Closures

Proposed § 106.40(a) specifies that the only substances that may be used in infant formulas are food ingredients that are generally recognized as safe (GRAS) for use in infant formula, that are used in accordance with the agency's food additive regulations, or that are authorized by a prior sanction issued by FDA. Under section 412(b)(2)(A) of the act, FDA is to establish CGMP's that it determines are necessary to ensure that the infant formula is manufactured in a way that is designed to prevent adulteration of the formula. Unless the safety of the ingredients of an infant formula has been established, the formula is adulterated under section 402(a)(1) and (a)(2)(C) of the act. Thus, the agency has tentatively concluded that CGMP requires that the manufacturer ensure that the ingredients that it uses in its formula are safe and suitable.

Proposed § 106.40(b) requires that infant formula containers and closures not be reactive or absorptive so as to affect the safety of the infant formula, and that all packaging material that comes in contact with an infant formula be composed of authorized substances and be used in accordance with any prescribed limitations. Various regulations that authorize the use of a material in contact with the food product also set conditions and limitations on that use. Thus, the agency proposes to require that the manufacturer not only use only materials specified in proposed § 106.40(b), but also that the materials be used as specified in the regulations authorizing their use. This provision will ensure that the food contact surface of containers and closures will not adulterate the infant formula.

In order for the manufacturer to maintain a complete record of how each ingredient, container, or closure was used and to determine which lots of infant formula are adulterated if a problem is ultimately identified with a particular lot of ingredients, containers, or closures, FDA is proposing, in § 106.40(c), that they be identified with batch or lot numbers. This batch or lot number can be used to identify ingredients, containers, or closures that have been released for use in infant formula or rejected for use in infant formula manufacture. It also can be used to track the ingredients, containers, or closures that were used in the manufacture of each batch of infant formula.

Proposed § 106.40(d) requires that infant formula manufacturers develop written specifications that stipulate the standards for acceptance or rejection of ingredients, containers, and closures. Stipulating the standards for acceptance or rejection of ingredients used to supply nutrients is important to ensure that all the required nutrients are present in the formula at the required levels. For example, the level of endogenous nutrients that a manufacturer expects will be supplied by an ingredient should be stipulated as a standard for acceptance or rejection of that ingredient. Endogenous nutrients are nutrients provided as a part of other nutrients, such as minerals provided as a part of the protein source. Sodium, for example, is frequently provided as part of the protein ingredient "caseinate."

To ensure that the mineral is provided in the infant formula at at least the minimal level, and not above the maximum level, required by § 107.100, the infant formula manufacturer must know what amount of a mineral is provided to the formula by all ingredients that are sources of the mineral. Thus, a standard for the level of the endogenous nutrient that is to be provided by an ingredient is an appropriate specification for the manufacturer to develop. If the level of the mineral is too high in the ingredient, it may cause the formula to exceed the maximum established in § 107.100. Similarly, if the level is too low, the formula may not meet the required minimal level.

Developing standards for acceptance or rejection of ingredients used in infant formula manufacture is also important to ensure that contaminants in the

ingredients that may lead to adulteration of the product are not present in the formula. Examples of contaminants that may lead to adulteration of an infant formula include certain heavy metals, such as lead. Infant formula manufacturers are currently setting standards for the lead in the ingredients that they use in infant formula to ensure that the lead level in infant formulas is at or below the quantification limit of the method used for lead determination (Ref. 32).

Stipulating the standards for acceptance or rejection of containers or closures used in infant formula manufacture is important to ensure that the integrity of the container and of the closure is maintained to prevent leakage of the formula and to prevent an infant formula from becoming adulterated, which can occur if the container or closure is not impenetrable to air (which can cause nutrient degradation), or if the container or closure allows outside contaminants to get into the infant formula.

Proposed § 106.40(d) also requires that manufacturers establish written specifications that stipulate the procedures for determining whether the ingredients, containers, and closures meet the standards. Examples of procedures manufacturers may use to determine whether they meet the standards are acceptance of a supplier's guarantee or certification and testing conducted by the infant formula manufacturer. In some cases, manufacturers must conduct their own testing to ensure that the standards for acceptance or rejection of the ingredient are met. For example, section 412(b)(3)(B) of the act requires that manufacturers test each nutrient premix for each relied-upon nutrient to ensure that the premix complies with its specifications or certifications by a premix supplier, but the act does not require testing of individual nutrient ingredients when such nutrients are not supplied as a nutrient premix. However, a manufacturer may find through experience that the best way to ensure that the final product will meet all specifications is to test certain nutrient ingredients for identity, purity, and potency before using them in the infant formula.

In addition, manufacturers should have controls in place to ensure that any ingredients, containers, or closures that do not meet any of their specifications are not used in production of a batch of infant formula. However, if these controls fail, and any such ingredients, containers, or closures are used in a batch of formula, FDA is proposing under § 106.40(d) that an individual qualified by training or experience conduct an investigation to ensure that the failure does not lead to release into the marketplace of an adulterated product.

Proposed § 106.40(e) requires that ingredients, containers, and closures be stored in areas clearly designated for materials pending release for use, materials released for use, or materials rejected for use in infant formula production in order to prevent mixups in using materials that are inappropriate for infant formula manufacturing. FDA is further proposing to require that any lot of ingredients, containers, or closures that does not meet the manufacturer's specifications be rejected and controlled under a quarantine system designed to prevent its use in the manufacture of infant formula. Failure to protect against the use of these materials would significantly increase the likelihood that an adulterated product will be produced.

Some ingredients used in infant formula are vulnerable to degradation when they are exposed to heat or air. Moreover, containers or closures may be exposed to air containing dust and dirt and become contaminated. Thus, the ingredients, containers, and closures may need to be reexamined after they are exposed to air, heat, or other conditions that may adversely affect them to ensure that they still meet the manufacturer's specifications. Thus, FDA is proposing, in § 106.40(f), to require retesting or reexamination after approved materials have been exposed to conditions that may adversely affect them.

Proposed § 106.40(g) requires that manufacturers make and retain records on ingredients, containers, and closures used in the manufacture of infant formula so that if adulteration of formula occurs, the manufacturer will be able to determine the source of the material, so that its use can be halted. In addition, the records will show the basis on which each ingredient, container, and closure was released for use in infant formula production, if questions about such release later arise. FDA has authority to require these records; under section 412(b)(4)(A)(i) of the act.

8. Controls to Prevent Adulteration During Manufacturing

The infant formula manufacturing process involves a number of complicated processes that may cause adulterated formula to be produced if the processes are not properly conducted or monitored. Therefore, FDA is proposing, under section § 106.50, to require that manufacturers establish controls to minimize the risk that manufacturing process errors will produce an adulterated or unsafe formula. The proposed requirements reflect many of the practices currently used by infant formula manufacturers and manufacturers of other commodities that require strict production controls to prevent product adulteration (e.g., Ref. 9 and 21 CFR 211.100 through 211.115).

Proposed § 106.50(a)(1) carries forward and amends the requirement in current § 106.25(a) that a master manufacturing order be prepared and followed. A master manufacturing order is necessary to ensure that the manufacturer will produce each batch of a particular infant formula the same way. If the master manufacturing order is not followed, all necessary ingredients may not be added to the formula in the appropriate concentrations and in the appropriate manner.

FDA is also proposing that manufacturers make and retain records that include complete information relating to the production and control of the batch at the time each manufacturing operation is performed (see proposed § 106.50(a)(2)). This proposed requirement will ensure that the complete history of each batch of infant formula is available for review in the event that a problem arises with a particular batch.

Proposed § 106.50(a)(2) also requires that an individual qualified by training or experience conduct an investigation of any deviations from the master manufacturing order and any corrective actions taken. This investigation is necessary to ensure that any deviations from the master manufacturing order do not lead to an adulterated product.

If any changes are made to the master manufacturing order, proposed § 106.50(a)(3) requires that they be drafted, reviewed, and approved by a responsible official and include an evaluation of the effect of the change on the nutrient content and the suitability of the formula for infants. This process is necessary to prevent unintended adverse effects that could result from changes to the master manufacturing order made by persons not qualified to assess their impact. The production of infant formula is a sophisticated process, and all organizational units that are involved in critical formulation and production steps, such as production, engineering, research, and regulatory affairs, should review and approve changes to the master manufacturing order. FDA has tentatively concluded, however, that all changes to the master manufacturing order need to be