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21 CFR Parts 106 and 107

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

36153

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to revise its infant formula regulations to establish requirements for quality factors and current good manufacturing practice (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. This action is being taken to improve the protection of infants that use infant formula products.

DATES: Comments by October 7, 1996, except that comments regarding information collection should be submitted by August 8, 1996. The agency proposes that any final rule that may issue based on this proposal become effective 120 days after its date of publication.

ADDRESSES: Submit written comments, data, or information to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857. Comments regarding information collection to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, ATTN: Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT: Carolyn W. Miles, Center for Food Safety and Applied Nutrition (HFS–456), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–401–9858.

SUPPLEMENTARY INFORMATION:

I. Background

A. The Infant Formula Act of 1980

In 1978, a major manufacturer of infant formula reformulated two of its soy products by discontinuing the addition of salt. This reformulation resulted in infant formula products that contained an inadequate amount of chloride, an essential nutrient for growth and development in infants. By mid-1979, a substantial number of infants had been diagnosed with hypochloremic metabolic alkalosis, a syndrome associated with chloride deficiency. Development of this syndrome in these infants was found to be associated with prolonged exclusive use of chloride-deficient soy formulas.

After reviewing the matter, Congress determined that, to improve protection of infants using infant formula products, greater regulatory control over the formulation and production of infant formula was needed, including modifications of industry's and FDA's recall procedures. Accordingly, Congress passed, and the President signed into law on September 26, 1980, the Infant Formula Act of 1980 (the 1980 act) (Pub. L. 96–359). This law amended the act to include section 412 (21 U.S.C. 350a).

In 1982, FDA adopted infant formula recall procedures, establishing subpart D of part 107 of its regulations (21 CFR part 107) (47 FR 18832, April 30, 1982), and infant formula quality control procedures (21 CFR part 106 (47 FR 17016, April 20, 1982)). In 1985, FDA further implemented the 1980 act by establishing subparts B, C, and D in 21 CFR part 107 regarding the labeling of infant formula, exempt infant formulas, and nutrient requirements for infant formula, respectively (50 FR 1833, January 14, 1985; 50 FR 48183, November 22, 1985; and 50 FR 45106, October 30, 1985).

B. The 1986 Amendments to the Infant Formula Act

In 1986, Congress, as part of the Drug Enforcement, Education, and Control Act of 1986 (the 1986 amendments) (Pub. L. 99–570) completely revamped section 412 of the act to address concerns that had been expressed by Congress and consumers about the 1980 act and FDA's implementation of that statute. These concerns included whether the quality control testing, CGMP, recordkeeping, and recall requirements that FDA had adopted would prevent children "from ever again being threatened by defective baby formula" (Ref. 1). The 1986 amendments: (1) State that an infant formula is deemed to be adulterated unless it provides certain required nutrients, meets the quality factor requirements established by the Secretary of Health and Human Services (the Secretary) (and, by delegation, FDA), and is manufactured in accordance with CGMP and quality control procedures established by the Secretary; (2) require that the Secretary issue regulations establishing requirements for quality factors and CGMP, including quality control procedures; (3) require that infant formula manufacturers regularly audit their operations to ensure that those operations comply with CGMP and quality control procedure regulations; (4) expand the circumstances in which manufacturers must make a submission to the agency to include when a manufacturer makes major changes in an infant formula, and when a manufacturer makes changes that may affect whether the formula is adulterated; (5) specify the nutrient quality control testing that must be done on each batch of infant formula; (6) modify the infant formula recall requirements; and (7) give the Secretary authority to establish requirements for retention of records, including records necessary to demonstrate compliance with CGMP and quality control procedures.

In 1989, the agency responded to the provisions of the 1986 amendments on recalls (sections 412(f) and (g) of the act) by establishing subpart E in part 107 (54 FR 4006, January 27, 1989). In 1991, the agency adopted infant formula record and record retention requirements that implemented the 1986 amendments by revising § 106.100 (56 FR 66566, December 24, 1991).

Although the agency has adopted regulations that respond to a number of the provisions of the 1986 amendments, it has not issued regulations on infant formula CGMP and quality factors or revised the notification procedures and quality control procedures to reflect the 1986 amendments. Since the passage of the 1986 amendments, agency representatives have visited infant formula plants to observe the manufacturing practice and quality control procedures that they employ, and the agency has solicited and received recommendations on CGMP from the Infant Formula Council. In addition, FDA has contracted with the Committee on Nutrition of the American Academy of Pediatrics (CON/AAP) to obtain expert advice on clinical testing of infant formulas with respect to the quality factor requirements. Moreover, both industry and the agency have

increased experience with the quantity and quality of information that should be submitted to meet the notification requirements of section 412(c) and (d) of the act.

This proposal addresses CGMP, quality control procedures, quality factors, and notification procedures and incorporates information resulting from the interactions between FDA and industry and between FDA and AAP. This proposal updates the language in part 107 to reflect the 1986 amendments and the November 1992 reorganization of the Center for Food Safety and Applied Nutrition (CFSAN).

C. FDA's Regulations on Nutrient Requirements

Section 412(i) of the act includes a table that lists nutrients that every infant formula must contain. This section also establishes a minimum level for each of the listed nutrients and a maximum level for eight of the listed nutrients. In addition, section 412(i)(2) of the act grants the Secretary (and by delegation FDA) the authority to revise the list of nutrients in section 412(i), and the minimum and maximum levels of those nutrients, by regulation. In the Federal Register of October 30, 1995, FDA established the nutrient requirements for infant formulas in § 107.100 (50 FR 45106). For the purpose of this document, the nutrients that are required to be in infant formula under § 107.100 will be referred to as "required nutrients," and the levels of these required nutrients established in § 107.100 will be referred to as "required levels."

II. The Need for Regulation

Relative to per unit of body weight, nutrient requirements are generally greater in infancy than at any other time during life. During the first year, the rate of growth is at its maximum, with birth weight typically doubling by 4 months of age and tripling by 1 year (Refs. 2 and 3). Moreover, the metabolic rate in infants is greater, and the turnover of nutrients is more rapid, than in adults (Ref. 4). Thus, infants must ingest adequate nutrients to support a rapid rate of growth and of developmental changes and to supply maintenance needs. Without adequate nutrition, infants would be unable to achieve their genetic potential for growth and development.

These nutritional needs must be met in early infancy by food in liquid form. Sucking and involuntary swallow reflexes are the mechanisms by which very young infants ingest food until teeth and motor coordination develop. Consequently, for infants who are not fed breast milk, infant formula often serves as the sole source, or the major source, of nutrition during this time of rapid growth and development.

Therefore, the importance of proper infant formula manufacture, composition, and nutrient levels cannot be overstated. Senator Metzenbaum explained why infant formula needs more regulation than other foods when he stated "there is simply no margin for error in the production of baby formula. An infant relies on the formula to sustain life and provide the proper nourishment at a time of rapid physical and mental development" (Ref. 1). The requirements contained in this proposal are designed to ensure that the formula fed to American infants fulfills its important function.

The CGMP and quality control procedures that FDA is proposing are designed to prevent the production of an adulterated infant formula. Defining CGMP will help to ensure that all of the required nutrients are included at appropriate levels in the formula, and that the formula is not contaminated with microorganisms or other materials that may be harmful to the infant.

Quality control procedures are designed to ensure that an infant formula contains the nutrients that are necessary to support growth and development, at the appropriate levels, not only when it enters into commerce but throughout its shelf life. FDA is proposing that each batch of infant formula be tested for all required nutrients and any nutrient added by the manufacturer, and that finished batches be periodically sampled and tested for nutrients throughout the shelf life of the product.

Quality factors are designed to ensure that the required nutrients and any nutrient added by the manufacturer actually reach the infant in a useable form. Quality factors "pertain to the bioavailability of a nutrient and the maintenance of level or potency of nutrients during the expected shelf life of the product" (Ref. 5). The 1986 amendments directed that the Secretary, by regulation, "establish requirements for quality factors for infant formulas to the extent possible consistent with current scientific knowledge, including quality factor requirements for the nutrients required by (section 412(i) of the act)."

In 1986, FDA advised Congress that the technology and science with respect to quality factors was still evolving, and that it was only possible to establish a quality factor for one nutrient. The agency said that it had already done so. However, in the 1986 Congressional Record (Ref. 1), Senator Metzenbaum stated that "the legislation contemplates that the Secretary will move to promptly develop and issue appropriate quality factor standards for different nutrients as the state of the science progresses." Since that time, as stated above, FDA has contracted with CON/AAP to obtain expert advice on quality factors; i.e., on the clinical testing of infant formula with respect to its nutritional safety and suitability for term infants.

In 1988, CON/AAP submitted a report (Ref. 6) under the contract that identified and discussed the types of clinical studies that might be considered for evaluation of the nutritional suitability of a formula for normal term infants. FDA has reviewed this report and the available scientific literature and has identified quality factors for protein and for complete infant formulas. The agency is proposing to adopt these quality factors as part of these regulations.

FDA has received numerous inquiries from industry for specific guidance on what information must be submitted to meet the requirements of sections 412(c) and (d) of the act, which state when a manufacturer must register with, submit to, or notify the agency about a new or changed infant formula, and what must be in the registration, submission, or notification. The agency is responding to these requests in this proposal. The agency is providing this information not only in response to these inquiries but also to facilitate more consistent registrations, submissions, and notifications. The lack of consistency in the format and content of registrations, submissions, and notifications has caused inefficiencies and delays in the agency's review. Accordingly, the agency is proposing to establish a consistent format and content for infant formula registrations, submissions, and notifications.

Within the past year, FDA has investigated a number of instances in which infant formula manufactured in the United States has been diverted from normal distribution channels and relabeled, sometimes with counterfeit labels for the same brand of infant formula but in other instances with counterfeit labels for different formulations. Infant formula bearing counterfeit labels is a potentially serious public health problem. It could cause infant formula that is past the use by date to enter the marketplace if the counterfeit label bears an incorrect use by date. The more serious consequence of this practice, however, is that it could cause infants that are intolerant to certain infant formula ingredients to be fed an incorrect formula, with serious consequences to the health of the infant,

if an infant formula has been relabeled with an incorrect label (e.g., a milk-based infant formula relabeled to indicate that it is a soy-based infant formula). Therefore, as part of this proposed regulation, the agency is requesting comments on new or modified procedures or controls that could be instituted during the labeling, packaging, or distribution of infant formula and that would be effective in preventing or reducing the potential for the diversion of infant formula from normal distribution channels and its relabeling with counterfeit labels.

III. Scope of this Document

To implement the 1986 amendments, the agency is proposing to amend its regulations by adding new subparts B, D, and E to part 106 and by redesignating existing subparts B, C, and D as subparts C, F, and G. Table 1 sets out the current and proposed subpart designations.

TABLE 1

Subparts	Current regulation	Proposed regulation
A	General Provisions	General Provisions.
B	Quality Control Procedures for Assuring Nutrient Content of Infant Formulas.	Current Good Manufacturing Practice.
C	Records and Reports	Quality Control Procedures.
D	Notification Requirements	Conduct of Audits.
E	None	Quality Factors for Infant Formulas.
F	None	Records and Reports.
G	None	Registration, Submission, and Notification Requirements.

The proposed regulation adds a new § 107.1 and will amend § 107.10(a)(2) by requiring that "any nutrient added by the manufacturer" be listed on the label. The proposed regulation amends §§ 107.240 and 107.250 by changing the reference to the Division of Regulatory Guidance to the Division of Enforcement to reflect the November 1992 reorganization of CFSAN.

IV. The Proposed Regulations

A. General Provisions

To reflect the expanded scope of the proposed regulations, FDA is revising the heading of part 106 to read, "Infant Formula-Requirements Pertaining to Current Good Manufacturing Practice, Quality Control Procedures, Quality Factors, Records and Reports, and Notifications."

1. Status and Applicability of the Regulations in Part 106

Proposed § 106.1 sets out the authority for each of the proposed subparts and the consequences under the act of failure to comply with any of the regulations in the proposed subparts. FDA is including proposed § 106.1 because it is important for manufacturers to be aware of the legal consequences of failure to comply with these regulations, which are being issued to implement specific sections of the act.

2. Definitions

The agency is proposing to amend § 106.3 by adding several definitions that are needed to explain activities that specifically concern the infant formula industry. It is important whenever possible to maintain consistent terminology throughout the agency's regulations. Therefore, as described in detail below, FDA has relied, where possible, on existing definitions in 21 CFR parts 105, 110, and 210 in arriving at these proposed definitions. Other definitions were derived from specific provisions in the act.

Proposed § 106.3(a), (g), (h), and (p) incorporate into part 106 the definitions for "batch," "lot," "lot number, control number, or batch number," and "representative sample" derived from 21 CFR 210.3(b)(2), (b)(10), (b)(11), and (b)(21), respectively. In addition to promoting consistency in the agency's regulations, FDA has tentatively determined that use of these definitions in part 106 is appropriate because they permit the agency to refer to the product in terms that reflect the fact that it is produced in bulk rather than on a unit-by-unit basis.

Proposed § 106.3(k), (q), and (r) incorporate into part 106 the definitions for "microorganisms," "shall," and "should" from 21 CFR 110.3(i), (p), and (q), respectively. In addition to promoting consistency, these definitions reflect the generally recognized scientific or legal meaning of these terms.

Proposed § 106.3(c), (f), (j), and (n) incorporate into part 106 the definitions for "indicator nutrient," "in-process batch," "manufacturer," and "nutrient premix" from current § 106.3. The definition of "manufacturer" in proposed § 106.3(j) warrants particular note. In the past there has been some confusion about who is and who is not a manufacturer of infant formula. This definition makes clear that a manufacturer is not only a person who combines raw ingredients together to produce an infant formula but also is a person who reconstitutes or otherwise changes the physical or chemical characteristics of an infant formula or who packages or labels the product in a container for distribution. For example, the agency is aware of a firm that reconstitutes powdered infant formulas and puts the reconstituted formula in bottles to sell to hospitals. This definition makes clear that this firm is a "manufacturer."

Proposed § 106.3(d) incorporates into part 106 the definition for "infant" from 21 CFR 105.3(e).

In addition to the definitions derived from FDA's existing regulations, the agency is proposing to amend § 106.3 by adding definitions that are derived from the definitions provided by Congress in the act.

Proposed § 106.3(e) and (l) incorporate into part 106 the definitions for "infant formula" and "new infant formula" from sections 201(aa) (21 U.S.C. 321(aa)) and 412(c)(2), respectively.

Proposed § 106.3(e) defines "infant formula" as a food that purports to be or is represented for special dietary use solely as a food for infants by reason of its simulation of human milk or its suitability as a complete or partial substitute for human milk. The phrase "solely as a food for infants" is somewhat ambiguous. Where there is an ambiguity in a statutory provision, it is appropriate to look to the legislative history to determine the appropriate interpretation. In the legislative history of the Infant Formula Act, whenever the words "sole" or "solely" are used, they appear in the context of describing infant formula as the "sole" or primary source of nutrition for infants or babies. For example, in explaining how the

1980 act would change existing laws, then-Congressman Gore stated: "First it would require that any infant formula marketed in the United States as the sole source of nutrition for normal babies include minimum amounts of all essential nutrients." (Ref. 7.) Congressman Mottl stated that the 1980 act "is concerned with human lives at their most vulnerable stage. We are talking about food that may be the sole source of nourishment for infants." (Ref. 7.) This language and other similar language in the legislative history evidence that Congress intended the act to apply to any food that purports to be or that is represented as an infant formula, regardless of whether other possible uses of the product are suggested in its labeling. If the law only applied to foods that are represented only for use as infant formula, then manufacturers could easily evade the requirements of the act for infant formula by representing their products for a second purpose. Such an interpretation would be inconsistent with the remedial purposes of the infant formula provisions of the act.

Proposed § 106.3(b) incorporates into part 106 the definition for "final-product-stage" derived from section 412(b)(3)(E) of the act. FDA has modified the definition, however, by adding the phrase "due to processing" at the end of the definition to clarify that the final-product-stage is when the infant formula "is homogeneous and is not subject to further degradation due to processing" and to distinguish the point in time after which the formula is subject to further degradation during the shelf life of the product.

Proposed § 106.3(i) incorporates into part 106 a definition of "major change" that is derived from section 412(c)(2)(B) of the act, which states that "* * * the term 'major change' has the meaning given to such term in section 106.30(c)(2) of title 21, Code of Federal Regulations (as in effect on August 1, 1986), and guidelines issued thereunder" (Ref. 8). Proposed § 106.3(i) defines "major change" as it is defined in current § 106.30(c)(2). It also provides a number of examples of infant formulas deemed to differ fundamentally in processing or in composition. These examples are derived from the guidelines that were issued by the agency and were incorporated into the definition of "major change" in section 412(c) of the act by the 1986 amendments.

Proposed § 106.3(m) revises the definition for "nutrient" in current § 106.3(d) to reflect changes to the act made by the 1986 amendments. As stated above, the 1986 amendments moved the nutrient table from section 412(g) to section 412(i)(1) and moved the provision on promulgation of standards for nutrients from section 412(a)(2)(A) to section 412(i)(2). The proposed regulation references the new section numbers. Proposed § 106.3(m) also includes the statement that nutrients are substances determined to be essential by the Food and Nutrition Board of the National Research Council or by FDA. The agency is including this statement in the proposed definition to provide consistency with § 107.10(b)(5) on labeling nutrient information. This paragraph allows such information to include any vitamin or mineral in the formula, provided that the nutrient has been identified as essential by the National Academy of Sciences through its development of a recommended dietary allowance or an estimated safe and adequate daily dietary intake range, or the nutrient has been identified as essential by FDA through a Federal Register publication.

Proposed § 106.3(o) defines "quality factors." The definition that FDA is proposing derives from the language of the act and its legislative history. Section 412(b)(1) of the act states that the Secretary shall "establish requirements for quality factors for infant formulas * * *, including quality factor requirements for the nutrients required by subsection (i)." House Report 96-936 (Ref. 5) states that quality factors "pertain to the bioavailability of a nutrient and the maintenance of level or potency of nutrients during the expected shelf life of the product." The language of the act and the House report show that Congress intended that infant formulas marketed in the United States should not only be safe, and contain all of the nutrients required to support infant growth and health, but should provide those nutrients in a bioavailable form that will mean that, throughout its shelf life, the formula will support optimal infant growth and health.

Thus, quality factors encompass something different than the analyzable nutrient content of the finished infant formula. Quality factor requirements not only ensure that the nutrient potency and biological effectiveness of a formula, as formulated, are adequate to support healthy growth, but also that subsequent processing, ingredient interactions, and time do not reduce the biological effectiveness of a formula. Quality factor requirements also ensure that unsafe nutrient "super potencies" or by-products are not created from ingredient breakdowns or interactions caused by processing or time.

B. CGMP

1. Introduction

The agency is proposing to adopt a new subpart B to implement the CGMP requirements in section 412(b)(2) of the act. Proposed § 106.5 is introductory. It reflects FDA's tentative view that the CGMP requirements set out in subpart B are the minimum necessary to ensure that the infant formula that is produced contains all the requisite nutrients and is not otherwise adulterated.

To develop the proposed CGMP regulations, as stated above, agency representatives visited infant formula plants to observe the manufacturing practice that they employ, and the agency has solicited and received recommendations on CGMP from the infant formula industry through the Infant Formula Council (Ref. 9). The agency also is relying on its knowledge of industry manufacturing practices gained through inspections of infant formula manufacturing establishments, review of infant formula submissions received from industry since 1986, and monitoring of infant formula recalls.

The proposed CGMP regulations also are based in part on FDA's existing regulations concerning CGMP for foods (21 CFR part 110) and for drugs (21 CFR part 211). Because infant formulas are foods, they should, at a minimum, be manufactured in a manner that is consistent with CGMP for all foods under section 402(a)(4) of the act (21 U.S.C. 342(a)(4)). Moreover, infant formulas are often the sole source of nutrition for infants during a period of rapid growth and development and, hence, are used during a period of nutritional vulnerability. Thus, if the formula is to promote optimal infant health and growth, each batch of infant formula must provide the nutrients prescribed under section 412(i) of the act at the levels specified in that section, much like each batch of drugs must meet compositional requirements for active ingredients if they are to have their intended effect. Therefore, FDA has tentatively concluded that some of the manufacturing practices required of drug manufacturers are relevant to infant formula manufacturers.

2. Production and In-Process Control System

Section 412(b)(2)(B)(iii) of the act states that CGMP and quality control procedures shall include requirements for "in-process controls including, where necessary, testing required by CGMP designed to prevent adulteration of each batch of infant formula." In the past, manufacturers of infant formula have referred to production and in-

process control systems intended to ensure that required nutrients are included in the formula and to prevent adulteration by such terms as "quality control plans," "standard operating procedures," or "master manufacturing procedures." Infant formula manufacturers also have investigated adopting a system, known as the ISO.9000 series, developed by the International Organization for Standardization (ISO).

The agency is proposing to establish a framework in which decisions about the production of infant formula are left to the manufacturer but that charges the manufacturer with incorporating into its production process measures that are designed to ensure the safety and nutritional quality of the formula.

For example, 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. This provision is a performance standard for determining how many employees are necessary, i.e., that there be enough to achieve, maintain, and document CGMP. FDA is not proposing to provide the specific number of employees required, the specific type of training that they must have, the specific task they are to perform, or the specific method by which records are to be kept.

In another example, proposed § 106.35(b)(4) requires that infant formula manufacturers ensure that automatic (mechanical or electronic) systems are validated before their first use to manufacture commercial product. However, in this provision, the agency is not stipulating any standards or specifications for the validation process because the extent of the validation that is necessary is related to the level of risk that each component of the system presents. These decisions about the validation necessary are left to the infant formula manufacturer to make.

As a third example, proposed § 106.91(b) requires that the manufacturer conduct nutrient stability testing at the beginning, midpoint, and end of the shelf life of the infant formula and with sufficient frequency to ensure that the formula complies with § 107.100 throughout its shelf life. Because manufacturers have experience with the nutrient stability of the infant formula matrices that they produce and are in a position to determine how frequently testing is necessary, the agency is proposing only to require testing "with sufficient frequency," instead of specifying what frequency is required.

Proposed § 106.6(a) requires that infant formula manufacturers comply with the requirements of subpart B of part 106 by implementing a system of production and in-process controls that covers all stages of processing, from receipt and acceptance of raw materials, ingredients, and components through storage and distribution of finished product, and that is designed to ensure that all requirements of subpart B of part 106 are met.

Infant formula manufacturing requires a degree of sophistication (e.g., in research and development, production equipment and procedures, and analytical equipment and methodology) that a vast majority of companies in the food processing industry do not have. A manufacturer must maintain constant control because a seemingly innocuous change in formulation or in a preparation method, or exposure to an unanticipated environmental condition, could create a health hazard. Moreover, infant formula manufacturers must be concerned not only that something is present in the formula that may adulterate that formula, such as a contaminant or a level of a required nutrient that exceeds the maximum level allowed by § 107.100, but also that something is absent from the formula, such as the lack or unavailability of a required nutrient. For example, the lack of a nutrient or the unavailability of an added nutrient has been responsible for a number of documented problems that have occurred in infant formulas (Ref. 1). Thus, FDA has tentatively concluded that the use of a production and in-process control system covering all stages of processing is necessary to ensure that the infant formula is manufactured in a manner that will prevent adulteration of the infant formula.

Proposed § 106.6(b) requires that the production and in-process control system be set out in a written plan, or set of procedures, that is designed to ensure that the infant formula is manufactured in a manner that will prevent adulteration of the formula. FDA has tentatively concluded that requiring that the production and in-process control system be set out in a written plan or a set of procedures is necessary to provide consistency in production of different batches of infant formula and to facilitate the preparation of each batch of infant formula. Consistency is provided because the plan means that there is a single set of procedures established that are to be followed in producing the formula. The plan also facilitates preparation of the formula because, given the sophistication of the infant formula manufacturing process, a written plan to which ready and easy reference can be had is essential. The importance of a written plan is well-recognized by industry. The use of a written plan or set of procedures for production of a batch of infant formula is already a wide-spread practice.

The agency has sought to develop a basic list of items that a firm would need to consider in developing its plan or procedures, but the agency is reluctant to offer such a list at this stage of the rulemaking, before it has received comments on the proposed good manufacturing practice regulations. The agency requests comments on whether such a basic list, over and above the provisions of Subpart B itself, is possible or desirable, and if it is, what such a list should include.

The agency would conceive of such a list, at a minimum, as consisting of a number of items. It would need to direct the manufacturer to establish the safeguards that it will rely upon to protect against the foreseeable sources of adulteration in the production of infant formula. It would also need to direct the manufacturer to establish procedures for ensuring that the manufacturing process functions properly. Several of the procedures that would have to be established to do so are defined in the proposed regulations, including: (1) Procedures, in accordance with proposed § 106.35(b)(2), to calibrate, inspect, and check hardware; (2) specifications, in accordance with proposed § 106.40(d), for the acceptance or rejection of ingredients, containers, and closures used in infant formula manufacture; (3) the master manufacturing orders in accordance with proposed § 106.50(a)(1); and (4) testing procedures, under proposed § 106.55(b), to ensure that powdered infant formula complies with the microbiological quality standards. Other items that would also seem to be appropriately included on such a list would be procedures for controlling the release of product, for ensuring its traceability, and for conducting GMP audits. However, FDA requests comments on whether these items provide an adequate checklist for the development of the type of written plan that is necessary under these proposed regulations.

For now, FDA is leaving the specific content of the procedures that are in the written plan to the manufacturer's discretion. FDA requests comment on whether the agency should develop guidance on the content of any of the