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I. Introduction and Summary

A. Introduction

FDA has examined the impacts of this interim final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct Agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity).We believe that the interim final rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. According to our analysis, we believe that the interim final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that Agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $141 million, using the most current (2012) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this interim final rule to result in any 1-year expenditure that would meet or exceed this amount.

The analyses that we have performed to examine the impacts of this interim final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act, and the Unfunded Mandates Reform Act of 1995 are included in this RIA.

B. Summary of Costs and Benefits

The estimated cost of the interim final rule is $7.29 million in the first year and $4.06 million in subsequent years. The estimated benefit to public health from this interim final rule is $10.00 million annually, resulting in total net benefits of $2.71 million in the first year and $5.94 million in subsequent years.

Benefit and Cost Overview (in millions)

	Benefits	**Costs**	**Net Benefits**
Total First Year	$10.00	$7.29	**$2.71**
Annual Total After the First Year	$10.00	$4.06	**$5.94**

II. Regulatory Impact Analysis for Interim Final Rule

A. Need for this Regulation

This interim final rule addresses current good manufacturing practices, quality control procedures, quality factors, records and reports, and notification procedures for infant formula. The need for these regulations is demonstrated by the history of problems with infant formula.

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, a nutrient essential for growth and development in infants. On July 26, 1979, three infants were diagnosed with hypochloremic metabolic alkalosis, a syndrome associated with chloride deficiency. Ultimately, a total of 141 related cases were identified. Symptoms of metabolic alkalosis are irritability, rapid heart rate, irregular heartbeats, and a drop in blood pressure. Development of this syndrome in these infants was found to be associated with prolonged, exclusive use of chloride-deficient soy formulas (Ref. 1). Congress subsequently determined that greater regulatory control over the formulation and production of infant formula was needed to provide better protection for infants fed formula and enacted the Infant Formula Act of 1980 (the 1980 act), which added section 412 to the FD&C Act. In 1986, Congress, as part of the Anti-Drug Abuse Act of 1986 (Public Law 99-570), addressed concerns that had been expressed by Congress and consumers about the Infant Formula Act and FDA's implementation relating to the sufficiency of quality control testing, CGMP, recordkeeping, and recall requirements.

The 1986 amendments: (1) Provide that an infant formula is deemed to be adulterated if it fails to provide certain required nutrients, fails to meet quality factor requirements established by the Secretary (and, by delegation, FDA), or if it is not processed in compliance with the CGMP and quality control procedures established by the Secretary; (2) require the Secretary to issue

regulations establishing requirements for quality factors and CGMP, including quality control procedures; (3) require infant formula manufacturers to audit their operations regularly to ensure that those operations comply with CGMP and quality control procedure regulations; (4) require a manufacturer to make a submission to FDA when there is a major change in an infant formula or a change that may affect whether the formula is adulterated; (5) specify the required nutrient quality control testing for each production aggregate of infant formula; (6) modify the infant formula recall requirements; and (7) authorize the Secretary to establish requirements for records retention, including records necessary to demonstrate compliance with CGMP and quality control procedures. In 1989, the Agency implemented the provisions on recalls (section 412(f) and (g) of the FD&C Act) by establishing subpart E in 21 CFR part 107 (54 FR 4006, January 27, 1989). In 1991, the Agency implemented the provisions on records and record retention requirements by revising 21 CFR 106.100 (56 FR 66566, December 24, 1991).

Section 412 of the FD&C Act requires the Secretary, and by delegation, FDA, to establish good manufacturing practices for infant formula that FDA determines are necessary to ensure that an infant formula is manufactured in a manner designed to prevent the adulteration of the formula. Such practices include microbial testing requirements for powdered infant formulas. Reports published in 2004 and 2006 (Refs. 2 and 3) identify Cronobacter (then classified as Enterobacter sakazakii*)* as a pathogenic microorganism of concern in powdered infant formulas. The data in table 1 show the association between the use of powdered infant formula and Cronobacter infections in infants reported since 1988 (Ref 4, Ref 5). CDC also analyzed data on 46 Cronobacter infections reported from 1961-2005 (Ref. 4). These data include the cases reported to FDA during the period 1988-2005 (see table 1). In 26 of the 46 cases, information on the type of feeding was available. Bowen and Braden (Ref. 4) reported

that 24 of these 26 infants (92 percent) were fed powdered infant formula.

The incidence of meningitis (the inflammation of the lining of the brain) in infants was first causally linked to consumption of powdered infant formula in one infant in 2002 (Ref. 6). Cronobacter can cause sepsis (bacteria in the blood), meningitis, or necrotizing enterocolitis (severe intestinal infection), particularly in susceptible populations including preterm infants, young infants, and those with compromised immune systems (Ref. 2).

Table 1.--Cronobacter Illnesses in the U.S. Associated with the Use of Powdered Infant Formula: 1988-2009

Year	Cases
1988	2
1989	3
1990	1
1991	1
2000	1
2001	1
2002	1
2003	1
2004	1
2005	3
2006	3
2007	2
2008	0
2009	1

In infants, sepsis caused by Cronobacter is characterized by fever or hyperthermia, lethargy, and poor feeding (Ref. 7). It may rapidly progress to hypotension and total vascular collapse. Despite treatment, the infection may lead to multiple organ failure and death (Ref. 8). Meningitis caused by Cronobacter is characterized by cerebral abscess formation and severe neurological impairment (Ref. 8). Other symptoms of meningitis that may be associated with a Cronobacter infection include destruction of the frontal lobes of the brain, liquefaction of cerebral white matter, and severe neurological complications, such as brain abscesses and convulsions. Necrotizing enterocolitis is a disease of the digestive tract in neonates and may be associated with Cronobacter; initial signs of this disease include feeding intolerance, increased gastric residuals, abdominal distension, and bloody stools (Ref. 9). Necrotizing enterocolitis may progress rapidly to intestinal perforation and peritonitis resulting in systemic collapse requiring surgery, intensive medical support, or both. The mortality rate for infant Cronobacter infections of all types may be as high as 40 to 80 percent (Ref. 4).

The data in table 1 show that, on average, there were about two illnesses per year for the

period 1988-2009. However, underreporting always complicates the estimation of foodborne illness. To correct for underreporting, certain factors may be applied. For example, in one study, Mead, et al. (Ref. 10) estimated an underreporting correction factor ranging from two illnesses for every one illness reported for very severe illnesses such as botulism to 38 illnesses for every one illness reported for the often milder illness associated with Salmonella. Given the extreme severity of illness associated with Cronobacter, FDA uses an underreporting correction factor of two. Thus, FDA estimates that there are annually, on average, four cases of infant illnesses associated with Cronobacter in the United States.

The estimated four cases per year of Cronobacter associated with powdered infant formula and the apparent increase in the number of cases over the last decade may indicate that the infant formula industry's current voluntary pathogen testing and good manufacturing practice activities are not sufficient to provide the protection necessary for products that serve as the sole source of nutrition for infants. FDA believes that the provisions of this interim final rule will address weaknesses in production that may result in the contamination of powdered infant formula with Cronobacter, which can lead to illness and death. The interim final rule's good manufacturing practices and quality control procedure requirements for powdered infant formula are especially important because such formula is an ideal medium for bacterial growth and because infants are at high risk of foodborne illness because of their immature immune systems. Furthermore, establishing requirements for quality factors will provide assurance that infant formulas containing new ingredients support normal physical growth and provide sufficient biological quality of protein. That is, as a sole source of nutrition, an infant formula supports the healthy growth of infants.

B. Characteristics of the Infant Formula Industry

The infant formula industry in the United States is characterized by a small number of firms; all firms manufacturing infant formula for introduction into interstate commerce must register with FDA. As of the time of this publication, this rule establishes requirements that will impact four current infant formula manufacturers, a total of 21 plants, and about 59 different formulations of infant formula (or about 15formulations per firm).[1] Estimated U.S. infant formula sales in 2007 were $3.5 billion (for an average of $700,000,000 for each of the five manufacturers in existence at that time), with 98 percent of all sales concentrated among three firms (Ref. 11). None of the four firms currently on the market is considered small.

C. Summary of the Economic Analysis of the Proposed Rule

The economic analysis of the 1996 proposed rule did not quantify any health benefits that would result from the implementation of the rule. The Agency did not receive any comments on estimating benefits.

Regarding the costs of the proposed rule, the analysis of the proposed rule stated that some infant formula manufacturers may not have been in compliance with two of the proposed CGMP requirements (61 FR 36203). The first area identified was controls to prevent adulteration caused by equipment or utensils. The economic analysis of the proposed rule did not quantify the cost to industry of establishing procedures to meet this proposed requirement. The second area identified in the proposal was controls to prevent adulteration due to automatic, mechanical, and electronic equipment. The analysis of the proposed rule characterized the cost of this requirement as the cost of the additional analysis of software modifications and was estimated to be approximately $100,000 per year for all plants in the infant formula industry.

[1] The number of different formulations of infant formula is smaller than the number of different infant formula products sold in the market. For a given formulation of infant formula, the end products can vary by, for example, whether the formulation is in a powdered or liquid form.

In addition to associating costs with particular proposed CGMP requirements, the Agency also associated costs with two general types of activities: recordkeeping and administrative costs. The analysis of the proposed rule estimated the total infant formula industry costs associated with additional recordkeeping as approximately $450,000 per year. Total infant formula industry administrative costs were estimated to be approximately $100,000 in the first year only. The analysis of the proposed rule did not associate costs with any other proposed requirement because the Agency believed that infant formula manufacturers' activities already adhered to all other proposed requirements.

The Agency received a number of comments on the costs of various provisions of the proposed rule. A summary of those comments and FDA's responses are provided in the cost analysis for this interim final rule.

D. Regulatory Options

In formulating the analysis of this interim final rule, four options were analyzed:

- Require the provisions of this interim final rule.
- Require the provisions of the proposed rule.
- Require only end-product testing for pathogens (§ 106.55), nutrient testing and stability testing (§ 106.91), growth monitoring studies for certain new infant formulas (§ 106.96), and new infant formula submissions (§§ 106.120 and 106.121).
- Require the provisions of this interim final rule, except a growth monitoring study as assurance for the quality factor of normal physical growth.

This analysis of the interim final rule provides estimates of costs and benefits for each of these options.

Data on current practices and costs in the infant formula industry are not available. FDA has relied on information provided by Donald L. Zink, Ph.D., an expert who is knowledgeable about the practices of the infant formula industry based on his experience working in private industry and in inspecting plants while at FDA (Ref. 12). FDA has also consulted with other professionals with experience in the infant formula industry in order to construct ranges for its estimates in certain sections of this analysis. In addition, FDA has relied on information regarding quality factors costs from Benson M. Silverman, M.D., a pediatrician with knowledge about the efforts required to comply with the interim final rule's quality factor requirements (Ref. 13).

There is one firm in the infant formula industry that produces infant formula that is not intended for domestic use. To the extent that this firm does not sell this formula in domestic commerce and exports this formula consistent with applicable requirements under sections 412 and 801 of the FD&C Act, the estimates presented in this analysis will be overstated.

1. Option 1: This Interim Final Rule

a. Costs of Option 1: Require the provisions of the interim final rule. The Agency received numerous comments on the costs of various provisions of the proposed rule. A summary of those comments and FDA's responses are provided here. Importantly, however, there were also areas where the Agency received no comments on the cost of compliance with the provisions of the proposed rule. In general, the Agency believes that firms in the infant formula industry already engage in practices consistent with most of the good manufacturing practice requirements of this interim final rule (Ref. 12). The relatively low number of illnesses, outbreaks, recalls, and FDA enforcement actions associated with infant formula despite the extreme vulnerability of infants is evidence that manufacturers are currently taking many

precautions to ensure the safety and quality of infant formula. However, some provisions of this interim final rule may cause manufacturers to incur additional costs. The annual mean costs of this option are summarized in table 2 and are then discussed by individual provision.

Table 2.--Annual Mean Costs of Option 1, By Provision

Provision Related to Current Good Manufacturing Practice (CGMP)	No. of Plants Not Currently in Compliance	No. of Manufacturers not Currently in Compliance	Estimated Cost[1]
§106.10	0	0	$0
§106.20 Bacteriological Testing	5	n/a	$13,000
§106.20 Radiological Testing	21	n/a	$2,625
§106.30	5	n/a	$3.1 million
§106.35 (non-recordkeeping)	0	0	$0
§106.40 (non-recordkeeping)	0	0	$0
§106.50 (non-recordkeeping)	0	0	$0
§106.55 (non-recordkeeping)	0	0	$0
§106.60	1	n/a	$39
§106.70	0	0	0
§106.80	0	0	0
§106.91	4	n/a	$31,000
§§106.90, 106.92, 106.94	5	n/a	$925
§§106.96, 106.120, 106.121[2]	n/a	n/a	$568,719
§106.100			$339,804
§106.110	0	0	0
§§ 106.130, 106.140	0	0	0
§106.150	0	0	0
Total Annual Mean Costs			$4,056,112

[1] Costs for GMP provisions are presented as means.
[2] Costs for quality factor provisions are estimated on a per infant formula basis.

i. Controls to prevent adulteration by workers (§ 106.10). The interim final rule requires infant formula manufacturers to employ sufficient personnel to ensure the operations are correctly and fully performed. In addition, the interim final rule requires personnel working directly with infant formula, infant formula raw materials, packaging, or equipment or utensil contact surfaces to practice good personal hygiene to protect the infant formula against

contamination. Finally, the interim final rule requires that any worker who reports having an illness or is observed to have an illness, an open lesion, or any other source of microbial contamination shall be excluded from direct contact with infant formula ingredients, containers, closures, in-process materials, equipment, utensils, and infant formula product until the condition is corrected or it is determined by medical personnel that the condition does not jeopardize the safety of the infant formula.

Based on expert opinion, it is estimated that current infant formula industry systems and processes adhere to the provisions of this section. Therefore, no cost is estimated for § 106.10.

ii. Controls to prevent adulteration caused by facilities (§ 106.20). The interim final rule requires infant formula manufacturers to establish controls to ensure that formula does not become adulterated as a result of the design and maintenance of formula production facilities. These controls include separating incompatible operations; establishing a system of segregation for raw materials, in-process materials, and final product; providing adequate lighting and ventilation; and providing appropriate toilet and hand washing facilities. This section also requires that the agents used within the facility, such as rodenticides, insecticides, and cleaning and sanitizing agents, be held and used so as not to contaminate formula, that culinary steam be used at certain production points, and that boiling water additives be used in conformance with the applicable food additive regulation (21 CFR 173.310). Finally, this section requires that potable water used in formula manufacturing meet EPA's Primary Drinking Water regulations, and that the water be tested for chemical, bacterial, and radiological contaminants at intervals specified in the interim final rule.

Based on expert opinion, 100 percent of infant formula plants do use culinary steam, as required by the interim final rule, and 100 percent of infant formula plants test water for

chemical contaminants as required by the interim final rule (Ref. 12). Therefore, no costs are estimated for these requirements. Although all plants regularly conduct basic water testing, professionals familiar with the infant formula industry estimate that no formula plants test for radiological contaminants as frequently as required by the interim final rule (i.e., once every 4 years) (Ref. 12). It is estimated that testing for radiological contaminants will cost $1,000 per plant, every 4 years or an average of $250/year ($1,000 divided by 4 years). For 21 plants, the estimated annual total cost is 21 plants x $250/year = $5,250 to comply with the requirement to test for radiological contaminants. Finally, FDA estimates that up to 25 percent of infant formula plants (about 5 of 21 plants) do not test weekly for bacteriological contamination (Ref. 12). For plants with systems or processes that do not adhere to this testing provision, this cost is estimated to be $100/week. For one plant, this testing is estimated to cost $5,200 annually. Therefore, five plants x $5,200 = $26,000 annually for these five estimated plants to comply with this testing requirement. However, another expert with industry experience believes that 100 percent of infant formula plants conduct routine testing for bacteriological contaminants; therefore, the lower cost estimate for this requirement is zero. Accordingly, the total annual estimated cost of § 106.20 is $31,250 ($26,000 for bacteriological testing + $5,250 for radiological testing), with a lower estimate of $5,250.

iii. Controls to prevent adulteration caused by equipment or utensils (§ 106.30). The interim final rule requires manufacturers to clean, sanitize, and maintain all equipment and utensils at regular intervals, have a qualified individual check that this activity has been done satisfactorily each time, and make and retain records that this activity has been completed.

(Comment 1) Some comments stated that significant costs would be associated with these requirements. Information provided by one firm indicated that requirements in this section

would likely cost approximately $1 million each year, per manufacturer. However, the comment did not provide support for this cost estimate.

(Response) The analysis for the proposed rule assumed that all firms already met these provisions and therefore, there were no additional costs associated with them (61 FR 36154 at 36203). Furthermore, professionals familiar with the infant formula industry with whom the Agency has consulted believe that current infant formula industry systems and processes largely adhere to the provisions in this section. However, FDA estimates that, conservatively, no more than 75 percent of formula plants, and perhaps none, presently have an appropriately qualified individual confirming that all cleaning, sanitizing, and maintenance has been satisfactorily completed. It is estimated that the same proportion of infant formula plants sufficiently document the required cleaning, sanitizing, and maintenance (Ref. 12). Thus, FDA agrees that there may be some costs associated with coming into compliance with this requirement.

Comments from the infant formula industry indicated that at least some, if not all, manufacturers clean, sanitize, and maintain equipment and utensils "frequently," in accordance with proposed § 106.30(f). One comment estimated that the cost of complying with § 106.30(f) is $1.24 million per year (i.e., $1 million adjusted for inflation). Because the comment did not state whether this estimate includes the costs of recordkeeping to demonstrate compliance with § 106.30(f), FDA interprets the comment conservatively as not including the costs of recordkeeping. Recordkeeping costs for this provision are addressed below in section discussing the cost of § 106.100.

For the 25 percent of infant formula plants that are not viewed as having systems and processes that adhere to this provision (5 of 21 plants), the total annual cost of preventing adulteration caused by equipment or utensils is estimated to be $6,200,000 ($1,240,000 x 5

plants). Because some infant formula professionals with whom FDA consulted believe that current infant formula industry systems and processes adhere to these provisions, the $6,200,000 estimate is considered an upper estimate, with the lower estimate being $0 (Ref. 12).

iv. Controls to prevent adulteration due to automatic equipment (§ 106.35). The interim final rule requires that manufacturers validate automatic (mechanical and electronic) equipment and make and retain records concerning the proper functioning of automatic equipment.

(Comment 2) Some comments stated that if automatic systems are to be validated before their first use to manufacture commercial product, this would require that whole batches of infant formula, worth up to hundreds of thousands of dollars each, be produced solely for validation purposes, only to be discarded. These comments asserted that the proposed rule's validation requirements will cost many millions of dollars to implement without adding consumer benefit and would take years to achieve.

(Response) FDA acknowledges that validation may be expensive. However, as discussed in the interim final rule, FDA has, in response to comments, revised § 106.35 to require that each system is validated prior to the release of any infant formula produced using the system. Thus, the interim final rule does not require that a production aggregate (batch) of infant formula be produced for validation purposes only and discarded.

(Comment 3) One comment stated that what constitutes the system validation requirements in proposed § 106.35 would provide a disincentive to make process improvements and quality and product innovations, because of what the comment characterized as an overreliance on CDER's drug CGMP model. For example, the comment pointed out that in proposed §106.35(a)(4), "validation" means establishing documented evidence that provides a high degree of assurance that a system will consistently produce a product meeting its

predetermined specifications and quality characteristics. In proposed § 106.35(b)(1), FDA proposed to require that all automatic systems be designed, installed, tested, and maintained in a manner that will ensure that these systems are capable of performing their intended function and capable of producing (including analyzing) infant formula in accordance with part 106 subparts B and C. The comment stated that, while these provisions are capable of an interpretation appropriate to infant formula, they are also capable of an interpretation more appropriate to pharmaceutical manufacture. Therefore, the comment asserted, requiring strict "drug-like" validation and revalidation of systems used to manufacture infant formula would be extremely costly, unnecessarily burdensome, and a disincentive for process improvements (i.e., improvements may not be implemented simply because of the burden of complex re-validation).

(Response) While the comment asserts that the validation requirement will be extremely costly and a disincentive for process improvements, no data are provided to support this assertion.

The analysis of the proposed rule estimated an industry-wide total cost of $100,000 for compliance with this section (61 FR 36154 at 36203). The Agency received a number of comments that claimed that the costs in the proposed rule were underestimated for this section, but provided no additional information.

The Agency acknowledges that what constitutes a reasonable level of validation activity will vary with the characteristics of the system in question and has revised the provisions of the interim final rule to require that a manufacturer need only validate those systems that affect points in the processing system that could result in an adulterated product, as set forth in section 412 of the FD&C Act. Furthermore, FDA estimates the cost of compliance with the system validation requirements is not likely to be as large as suggested by the comments. FDA

estimates that the all manufacturers in the infant formula industry sufficiently validate the automatic equipment used in the manufacture of infant formula, but that no more than 75 percent of such manufacturers sufficiently document the required validation and revalidation (Ref. 12). Therefore there are no costs associated with the non-recordkeeping requirements of § 106.35. Recordkeeping costs associated with § 106.35(c), in accordance with § 106.100(f)(5), are addressed in section II.D.1.a.xiv of this document .

v. Controls to prevent adulteration caused by ingredients, containers, and closures (§ 106.40). The interim final rule requires an infant formula manufacture to develop written specifications for ingredients, containers, and closures used in manufacturing and packaging infant formula and to develop written procedures to determine whether these specifications are met. When a specification is not met, the manufacturer shall review and document whether such failure adulterates the infant formula or could result in an adulterated formula.

(Comment 4) One comment expressed concern that under the proposed rule, endogenous nutrient levels should be included in ingredient specifications. The comment stated that some manufacturers do not currently conduct such testing on all ingredients. This comment stated that requiring all raw materials to be tested to determine all endogenous nutrient levels would have a significant impact on operating costs and, potentially, on product quality, with no increased benefit to consumers. The comment stated that it would be impractical to include specifications for contaminants in the raw materials specifications due to the sophistication and extremely high cost of the testing involved.

(Response) The interim final rule does not require that a manufacturer prepare written specifications for all nutrients in all raw materials or test for all nutrients in all raw materials. Instead, § 106.40(d) of the interim final rule requires that a manufacturer develop written

specifications for ingredients. Under § 106.6(c) of the interim final rule, a manufacturer must establish specifications to be met at any point, step, or stage in the production process where control is necessary to prevent adulteration. Such specifications may include those for nutrients in raw materials. Similarly, the interim final rule does not require that a manufacturer prepare written specifications for all potential contaminants in raw materials or test all raw materials for all potential contaminants. Rather, a manufacturer must determine the points, steps, or stages in the production process where control is necessary to prevent adulteration and establish specifications to be met. Such specifications may include those for contaminants, as appropriate. FDA has revised § 106.40(d) to require that a manufacturer develop written specifications for ingredients, containers, and closures used in infant formula manufacturing and packaging and develop and follow written procedures for determining whether the ingredients, containers, and closures meet these specifications. Furthermore, FDA has revised proposed § 106.40(d) to require that a manufacturer conduct a documented review and make a material disposition decision if any ingredient, container, or closure for which the manufacturer has established a specification is determined to deviate from such specification.

(Comment 5) Some comments stated that requiring that raw materials be tested for all endogenous nutrients will have a significant impact on laboratory space, manpower, and operating costs. In addition, the inclusion of routine contaminant testing in the infant formula industry would be grossly impractical due to the sophistication of testing involved and the exorbitantly high costs associated with compliance. The comment did not provide estimates of the cost of compliance with this provision of the proposed rule.

(Response) As noted previously in this document, the interim final rule does not require that a manufacturer prepare written specifications for all nutrients in all raw materials and for all

potential contaminants in such materials. Instead, the interim final rule requires the manufacturer to determine the specifications it must establish at any point, step, or stage in the production process where control is necessary to prevent adulteration (see § 106.6(c) of the interim final rule). Based on expert opinion, infant formula industry systems and processes already adhere to the overall requirements in § 106.40 (Ref. 12). That is, FDA assumes that all manufacturers currently establish specifications for ingredients, containers, and closures, and conduct a review and make and document a material disposition decision if such specifications are not met. Therefore, there are no costs estimated for this section of the interim final rule, with the exception of the records requirements which are addressed in this document.

vi. Controls to prevent adulteration during manufacturing (§ 106.50). The interim final rule requires a manufacturer to prepare and follow a written master manufacturing order that establishes controls and procedures for the production of an infant formula. It also requires a manufacturer to identify the contents, including the processing stage and the production aggregate number, of a production aggregate of infant formula, and of all compounding and storage containers, processing lines, and major equipment used during the production of a production aggregate of infant formula. In addition, this section requires a manufacturer to establish controls to ensure that the nutrient levels required for the formula are maintained, and that the formula is not contaminated with microorganisms or other contaminants.

(Comment 6) One comment on proposed § 106.50(c) stated that it is unclear what the Agency means by "identify" the contents of all compounding and storage containers, processing lines, and major equipment used during the production of a production aggregate of infant formula. The comment stated that if this means that operators need to document all the equipment that is being used, additional personnel will be needed along with a system to track

the equipment, and the resulting cost in manpower and interference with production timetables would be huge.

(Response) FDA notes that this comment did not provide any specific cost information for this provision except to characterize the costs as "huge."

As noted in the interim final rule, the term "identify" does not mean that a manufacturer needs to document or physically place labels on all equipment being used. Importantly, FDA has clarified the interim final rule to require a system of identification, and a manufacturer is free to determine the type of system to use to identify (i.e., distinguish) the contents of the compounding and storage containers, the processing lines, and major equipment in use during manufacturing. For example, manufacturers may use a bar code system for determining which ingredient goes where and when, and which equipment is used. Therefore, any costs associated with this provision will likely be insignificant and are not included in the analysis for the interim final rule.

(Comment 7) A comment stated that the wording in proposed § 106.50(f)(3) would have a significant financial impact on the manufacturer by requiring the rejection of all out of specification in-process materials.

(Response) The interim final rule does not require the rejection of all out of specification in process materials. Section 106.50(f)(1) of the interim final rule requires that an individual qualified by education, training, or experience conduct a documented review and make a material disposition decision to reject, reprocess or otherwise recondition, or approve and release the affected in-process material for use or distribution.

FDA estimates that, with the exception of the records requirements which are addressed below, there are no costs associated with the requirements set forth in § 106.50, based on the

information available to the Agency that infant formula industry systems and processes already adhere to such provisions (Ref. 12). Therefore, there are no costs estimated for this section of the interim final rule.

vii. Controls to prevent adulteration from microorganisms (§106.55). The interim final rule requires a manufacturer of powdered infant formula to test representative samples of each lot of powdered infant formula at the final product stage and before distribution to ensure that each lot meets the microbiological quality standard of negative in 30 x 10 g samples for Cronobacter and negative in 60 x 25 g sub-samples for Salmonella. FDA will determine compliance using methods described in the Agency's Bacteriological Analytical Manual (BAM). The microbiological testing requirements proposed in 1996 have been substantially changed in the interim final rule. The Agency received no comments regarding the costs of sampling and testing for Cronobacter and Salmonella spp.

FDA estimates that, with the exception of the records requirements, which are addressed below, there are no costs associated with the requirements in § 106.55, based on the Agency's understanding that infant formula industry systems and processes already adhere to such provisions (Ref. 12). Therefore, there are no costs estimated for this section of the interim final rule.

viii. Controls to prevent adulteration during packaging and labeling of infant formula (§106.60). The interim final rule requires that a manufacturer examine packaged and labeled infant formula during finishing operations to ensure that all containers and packages in the production aggregate have the correct label, the correct use-by date, and the correct code established under § 106.80. The labels must be designed to maintain their legibility and to stay attached to the infant formula container.

There are additional requirements for the labeling of multiple lot packages that will ensure that recalled products are traceable. Multiple lot packages that do not contain the same infant formula (mixed packages) may be assembled by diverters or manufacturers of hospital discharge packages and such mixed packages must have a means of being tracked. The multiple lot package may be assigned a unique identification number, provided that the manufacturer or distributor knows the contents of these packages, including the product name, the name of the manufacturer, distributor, or shipper, the code established under § 106.80, and a "use by" date that is no later than the "use by" date of the container exhibiting the closest "use by" date applied to satisfy the requirement of § 107.20(c). The intent of this provision is to permit traceability of formula products that are subject to a recall. Based on information in comments from the infant formula industry, it is estimated that the current identification practice for hospital discharge packages is already consistent with the requirements of § 106.60(c)(2)(ii).

FDA received one comment in 1996 on the proposed rule that asserted that "diverters" are legitimate businesses that provide goods, including infant formula, to wholesale and retail grocery, drug, and mass merchandise chains at competitive prices and are considered a part of the "normal distribution channels." These "diverters" generally purchase products in a geographic area where a special allowance or deal is being offered, repackage those goods (often in mixed lots), and then resell the products at a lower price in an area where the deals are not being offered.

Although the 1996 comment asserted that diverters may consolidate several lots of product into one shipping case, the experts consulted by FDA opined that it is likely that such repackaging is less frequent today than it was in 1996, but it is possible that that such repackaging of mixed lots may still occur with a very small amount of infant formula (Ref. 12).

Another infant formula industry expert with whom FDA consulted opined that diverters are not a mainstream outlet for infant formula. Both experts observed that food product distributors strive to retain case integrity in order to avoid the labor costs of reassembly, so market forces work against the practice of repackaging. This interim final rule will require diverters to label packaging (such as packing cases) to facilitate product tracing and to keep specific records of the distribution of these mixed lot cases. FDA estimates that there will be some minimal cost associated with this recordkeeping and labeling (Ref. 12). Thus, to the extent that there are infant formula diverters, they operate as part of the grey market and the burden on them from this provision is not known. To be conservative, based on expert opinion, it is estimated that, at most, 1 percent of infant formula may be handled this way.

The interim final rule will require diverters to properly label mixed lot cases and keep records of the distribution of these cases. For the purposes of this analysis, it is estimated that it may take one worker, at most, 15 minutes to relabel one case of infant formula, one time each month (.25 x 12 months = 3 annual hours), using manual methods, to meet the requirements of § 106.60(c)(2). At a wage of $26.24 per hour, including overhead (Ref. 14), the maximum cost of meeting the requirement of § 106.60(c)(2) is $26.24 x 3 = $78.72 per year.

ix. Controls on the release of finished infant formula (§106.70). This section of the interim final rule requires infant formula manufacturers to control the release of finished infant formula. Specifically, this section requires a quarantine system to prevent the distribution of infant formula until the manufacturer determines that the formula meets all applicable specifications or otherwise is not adulterated. Manufacturers are also required to clearly identify rejected infant formula as such and to hold it under a quarantine system. Based on expert opinion, it is estimated that current infant formula industry systems and processes adhere to the

provisions of this section (Ref. 12). Therefore, no costs are estimated for § 106.70.

x. Traceability (§ 106.80). This section of the interim final rule requires that each production aggregate of infant formula bear a code that identifies the product and the establishment where the product was produced to permit tracing of all stages of the manufacture of the production aggregate. FDA's current infant formula regulations (21 CFR 106.90) require all formula to be coded consistent with 21 CFR 113.60(c). Based on expert opinion, it is estimated that current infant formula industry systems and processes adhere to this section's provisions (Ref. 12). Therefore, no costs are estimated for § 106.80.

xi. General quality control (§ 106.91). This section establishes requirements for two types of quality control testing for infant formulas: nutrient testing and stability testing. For nutrient testing, the interim final rule requires certain testing of each production aggregate at four points in the production process: testing of each nutrient premix for each nutrient; testing no later than the final product stage and before distribution for an indicator nutrient from each nutrient premix; testing at the final product stage for vitamins A, C, E, and thiamin; and, at the final product stage, testing for all required nutrients and all nutrients added by the manufacturer for which the manufacturer has not previously tested the production aggregate.

Stability testing is designed to ensure that a formula's nutrients are present at the required level throughout the shelf life of the product. The level of nutrients must be provided on a consistent basis in every production aggregate because an infant consuming this product has no access to other foods or nutrient source. The only way that a manufacturer can determine whether a product contains all the nutrients in the required amount is to test for such nutrients. For an infant formula that is a new infant formula, the interim final rule requires the manufacturer to conduct initial stability testing by collecting from each manufacturing site and at

the final product stage a representative sample of the first production aggregate of each physical form (powder, ready-to-feed, or concentrate) in its final packaged form, and to evaluate the levels of all required nutrients and all nutrients added by the manufacturer. This testing is required to be repeated every 3 months throughout the shelf life of the product. If the shelf life of a new infant formula is not substantiated by such testing, the interim final rule requires that the testing be repeated or that the shelf life label of the product be revised. For subsequent production aggregates of a new formula, the interim final rule requires that the manufacturer collect, from each manufacturing site and at the final product stage, a representative sample of packaged, finished formula in each physical form (powder, ready-to-feed, or concentrate) and evaluate, at the beginning, middle, and end of the shelf life of the formula, the level of all required nutrients and any other nutrient added by the manufacturer. If this testing does not substantiate the shelf life of a subsequent production aggregate of infant formula, the interim final rule requires the manufacturer to investigate the cause of such variance and evaluate its significance, address any other production aggregates implicated by the testing results, and determine whether the initial stability testing should be repeated.

(Comment 9) Comments asserted that requiring that all nutrients (rather than just the ones that are subject to degradation) be tested throughout the formula shelf life would add significantly to the costs of infant formula, with no real benefit. One comment suggested that the proposed frequency of stability testing was excessive and did not correspond to current infant formula industry practice. This comment noted that some manufacturers routinely initiate a stability testing program during the development of a formula to assess its stability throughout the duration of the proposed shelf-life. This comment estimated additional costs of $24,000 per year per plant to comply with this requirement.

(Response) The interim final rule revises the stability testing requirements for infant formula and for new infant formulas. The interim final rule requires testing of each nutrient in any nutrient premix used in the manufacture of an infant formula that the premix is relied upon to provide to ensure that the premix is in compliance with the manufacturer's specifications (§ 106.91(a)(1)); the testing of each production aggregate of infant formula for at least one indicator nutrient for each of the nutrient premixes used to confirm the presence of the nutrients in the proper concentration (§ 106.91(a)(2)); the testing of each production aggregate at the final product stage for vitamins A, C, E, and thiamin (§ 106.91(a)(3)); and the testing of the production aggregate during the manufacturing process or at the final product stage for all nutrients required by § 107.100 to be included in such formula that have not already been tested for in the premix or that are already required to be tested at the final product stage, and other added nutrients not already tested as part of a nutrient premix (§ 106.91(a)(4)).

The interim final rule also requires that a manufacturer perform testing of representative samples of the first production aggregate of a new infant formula every three months for all nutrients required under § 107.100 and all other nutrients added by the manufacturer throughout the shelf-life of the product (§ 106.91(b)(1)). For all other formulas, the interim final rule requires that a manufacturer test a representative sample of each production aggregate at the final-product stage for all nutrients required under § 107.100 and all other nutrients added by the manufacturer, and also perform testing at the midpoint and at the end of the shelf-life of the product (§ 106.91(b)(2)).

If the results of the testing required by § 106.91(b)(1) do not substantiate the shelf life of the infant formula, the manufacturer is required either to repeat the initial stability testing on a subsequently produced production aggregate or to revise the shelf life label statement for such

product so that such statement is substantiated by the stability testing results (§ 106.91(b)(3)). If results of the testing required by § 106.91(b)(2) show that any required nutrient is not present in the production aggregate of infant formula at the level required by § 107.100 or that any nutrient added by the manufacturer is not present at the level declared on the label of the production aggregate of infant formula, the manufacturer must: (1) Investigate the cause of such variance in the level of any required or added nutrient; (2) evaluate the significance, if any, of the results for other production aggregates of the same formula that have been released for distribution; (3) address, as appropriate, all production aggregates of formula released for distribution that are implicated by the testing results; and (4) determine whether it is necessary to repeat the testing required by § 106.91(b)(1) (§ 106.91(b)(4)).

The cost of these general quality control requirements was not discussed in the economic analysis of the proposed rule. FDA estimates that 100 percent of infant formula manufacturers perform nutrient testing on each production aggregate as specified in this provision (Ref. 12). With respect to initial stability testing of new infant formulas, FDA estimates that 80 percent of the infant formula industry (about 17 of 21 plants) conduct such testing as specified in this regulation. Among the 20 percent of the infant formula industry that does not conduct the initial nutrient stability testing as specified in this rule (about 4 of 21 plants), FDA estimates that those four plants do conduct initial stability testing, but may not do so at the specified 3-month intervals (Ref. 12). With respect to the stability testing required by § 106.91(b)(2), FDA estimates that 100 percent of infant formula manufacturers conduct stability tests as specified in these provisions of the interim final rule.

FDA estimates that compliance with the general quality control provisions of the interim final rule will be half the cost estimate provided by the comment, that is, these requirements will

cost an additional $12,000 per plant per year, or $15,500 after adjusting for inflation. The total annual cost of general quality control then is $62,000 per year (4 plants x $15,500), which will act as an upper estimate of costs for this section of the interim final rule. Because other professionals familiar with the infant formula industry with whom the Agency consulted believe that current infant formula systems and processes adhere to or exceed the provisions of this section, FDA estimates, as a lower estimate, that the costs of this provision are $0.

xii. Audits and audit plans and procedures (§§ 106.90, 106.92, and 106.94). The interim final rule (§ 106.90) requires an infant formula manufacturer to conduct regularly scheduled audits to determine whether the manufacturer has complied with CGMP. The interim final rule (§ 106.92) also requires an infant formula manufacturer to conduct regularly scheduled audits to determine whether the manufacturer has complied with the quality control procedure requirements necessary to ensure that infant formula products provide required nutrients. Both types of audits are to be conducted by suitably qualified personnel at a frequency that is necessary to ensure compliance with the CGMP regulations.

The interim final rule also requires that a manufacturer develop and follow a written audit plan that includes procedures that set out the methods the manufacturer will use to determine whether the facility operates in accordance with current good manufacturing practice, with the required quality control procedures, and in a manner designed to prevent adulteration of the infant formula. The required audit procedures must include an evaluation of the production and in-process control system by: (1) Comparing the observed production process to the written plan, (2) reviewing records made where control is deemed necessary to prevent adulteration, (3) reviewing records showing how deviations from any specification were addressed, and (4) reviewing a representative sample of all records.

(Comment 9) One comment suggested that the requirement in proposed § 106.94 would make audits particularly tedious and result in overly prolonged audits. The comment added that this change would require additional trained personnel to complete this type of audit, and it would interfere unnecessarily with the focus on high quality production.

(Response) The cost of auditing was not addressed in the economic analysis of the proposed rule. FDA bases its estimates on the information provided to the Agency from professionals familiar with the infant formula industry. Based on this information, FDA estimates that the audit systems and processes of 100 percent of infant formula establishments adhere to the provisions in §§ 106.90 and 106.92 because they regularly conduct comprehensive compliance audits of their operations. In terms of the requirements for audit plans and procedures, FDA estimates that 75 percent of the infant formula industry (16 of the 21 plants) already adhere to the provisions of § 106.94 of the interim final rule but that 25 percent of infant formula plants (5 of 21 plants) do not conduct audits that conform to the procedures specified in § 106.94 of the interim final rule (Ref. 12). It is estimated that the ongoing review and updating of audit plans will require a senior validation engineer 8 hours at $46.26 per hour, including overhead (Ref. 15). Therefore, 8 hours x $46.26/hour = $370.08 and $370.08 x 5 plant = $1,850 for industry to comply with the requirements to regularly review and update audit plans. This cost will be an annual cost because the plan will need to be reviewed and updated at least annually to account for changes in processing.

xiii. Assurances of quality factors in new infant formulas, new infant formula submissions, and quality factor submissions (§§ 106.96, 106.120, and 106.121). This interim final rule requires that a manufacturer of a new infant formula conduct a growth monitoring study to demonstrate that an infant formula supports normal physical growth, unless the

manufacturer qualifies for an exemption from the need to conduct such a study (§ 106.96(b)). Some changes to a formula are not expected to affect the bioavailability of the nutrients in the formula, such as a change in the type of packaging for an existing infant formula. A manufacturer may request an exemption from the requirement for a growth monitoring study under certain circumstances. For example, a manufacturer may consider submitting such a request to FDA if it can provide assurances that an alternative method or study design is based on sound scientific principles and can be shown to support normal physical growth in infants, or that the change made by the manufacturer to an existing formula does not affect the bioavailability of the formula.

Infant formula manufacturers currently conduct infant growth monitoring studies under certain circumstances on a voluntary basis, and this interim final rule will largely codify this current industry practice. Based on the frequency of the introduction of new formulations and the current general infant formula industry practice of conducting growth monitoring studies, FDA believes that industry-wide compliance with § 106.96(b) will result, at most, in one additional infant growth monitoring study per year for new infant formulas (Ref. 13). Based on information from those familiar with the type of growth monitoring study required by this interim final rule, FDA estimates that a study complying with the interim final rule will cost $500,000 (Ref.13). This cost is presented in table 2 (Ref. 13). Furthermore, it is estimated that the cost of the one additional growth study will cover the recordkeeping costs associated with §§ 106.96(d) and 106.100(p)(1).

Under § 106.96(c)(1), an infant formula manufacturer may be exempt from the requirements of § 106.96(b) if the manufacturer requests an exemption and provides assurances, as required under § 106.121, that the changes to the infant formula are limited to changing the

type of packaging. Under § 106.96(c)(2), an infant formula manufacturer may also be exempt from the requirements of § 106.96(b) if the manufacturer requests an exemption and provides assurances, as required under § 106.121, that demonstrates to FDA's satisfaction, that an alternative method or study design is available to show that the formula supports normal physical growth in infants, that the change to an existing formula does not affect the bioavailability of the formula (including the bioavailability of its nutrients), or that the formulation is marketed in more than one form and the quality factor requirements are met by the form of the formula that is processed using the method that has the greatest potential for adversely affecting the nutrient content and bioavailability. The Agency estimates that 34 exemptions will be submitted annually and that each exemption will take 20 hours to assemble (Ref. 13). At a wage of $54.96 per hour, which is $36.64 per hour plus 50 percent for overhead, one exemption will cost $54.96 x 20 hours = $1,099.20 for one exemption (Ref. 16). Therefore, the cost to comply with § 106.96(c) is 34 exemptions x $1,099.20 = $37,372.80.

In some cases, the manufacturer of an infant formula that is not new infant formulas (i.e., an eligible formula, which could include infant formula currently on the market) may need to conduct a growth study of that formula. This is because under § 106.96(a) of the interim final rule, all infant formulas distributed in interstate commerce must meet the quality factor of normal physical growth. Section 106.96(i)(1) of the interim final rule provides criteria by which a manufacturer may demonstrate that an eligible formula meets the quality factor of normal physical growth. The interim final rule defines "eligible infant formula" (§ 106.3 of the interim final rule) as an infant formula that could have been or was lawfully distributed in the United States on the 89th day afterthe publication date of the interim final rule and establishes specific quality factor requirements for these formulas.

FDA completed a review of the data and information available to the Agency that is relevant to the ability of currently marketed eligible infant formulas to meet the quality factors, including the quality factor of normal physical growth. The Agency determined, based on the data reviewed, that for four of those infant formulas, the scientific information available to the Agency was not sufficient to show that these formulas meet the quality factor of normal physical growth (Ref. 13). Thus, the manufacturers of these four formulas may need to conduct a growth monitoring study that meets the criteria under § 106.96(i)(1)(i) or § 106.96(i)(1)(ii). Accordingly, it is estimated that, for these eligible infant formulas, four growth studies will be performed one time at a cost of $500,000 each or $2,000,000 total ($500,000 x 4 = $2,000,000). For purposes of this analysis, it is estimated that all growth studies performed on eligible formulas will occur in the first year following publication of the interim final rule. Furthermore, it is estimated that recordkeeping costs associated with these growth studies, and required by § 106.96(i)(4) and § 106.100(p)(2), will be covered by the estimated cost of conducting the growth studies. For the 46 eligible infant formulas for which no growth studies will be performed, the recordkeeping burden of §§ 106.96(i)(4) and 106.100(p)(2) is fulfilled by gathering of existing data into a record. For 46 eligible infant formulas, the cost of this activity is 46 eligible formulas x 20 hours per formula = 920 hours and 920 hours x $54.96 hourly wage = $50,563.20.

The requirement of § 106.96(f) states that a manufacturer shall meet the quality factor of sufficient biological quality of the protein by establishing such biological quality in the infant formula when fed as the sole source of nutrition using an appropriate modification of the Protein Efficiency Ratio (PER) rat bioassay. Under § 106.96(g)(1), a manufacturer of an infant formula may be exempt from this requirement if the manufacturer requests an exemption and provides assurances, as required under § 106.121, that changes made by the manufacturer to an existing

infant formula are limited to changing the type of packaging. Under § 106.96(g)(2), a manufacturer may also be exempt from the requirements of § 106.96(f) if the manufacturer requests an exemption and provides assurances, as required under § 106.121, that demonstrate, to FDA's satisfaction, that the change to an existing formula does not affect the bioavailability of the protein. FDA estimates that the infant formula industry will submit a total of 35 PER submissions each year for formulas that are not eligible infant formulas: 34 exemption requests and the results of one PER study (Ref. 13).

A PER study conducted according to AOAC Official Method 960.48 will be 28 days in duration. It is estimated that there will be 10 rats in the control and test groups (a total of 20 rats), and that food consumption and body weight will be measured at day zero and at 7 day intervals during the 28-day study period (a total of 5 records per rat). It is estimated that this additional PER study will cost $1,000 annually to fulfill the requirements of § 106.96(f) (Ref. 13), an estimate that includes costs related to the development of a written report of the PER study.

For the submission of the PER exemption for non-eligible infant formulas, it is estimated that industry will submit 34 exemptions per year and that each exemption will take support staff 12 hours at a wage of $27.23 per hour, calculated as $18.15 plus 50% for overhead (Ref. 17). Therefore, 12 hours x $27.23 wage per hour = $326.76 per exemption; $326.76 per exemption x 34 exemptions = $11,109.84 annually to fulfill the requirements of § 106.96(g).

Similarly, for eligible infant formulas, a manufacturer will be required by § 106.96(e) to meet the quality factor of sufficient biological quality of protein. However, the manufacturer may meet the quality factor of sufficient biological quality of protein by fulfilling any one of the criteria under § 106.96(i)(2). Section 106.96(i)(2) of the interim final rule provides that an

eligible formula meets the quality factor of sufficient biological quality of protein if: (i) The scientific evidence on such infant formula meets the requirements of paragraph (f) of § 106.96 that apply to an infant formula that is not an eligible infant formula; (ii) the scientific evidence on such infant formula is a study that establishes the biological quality of the protein in an infant formula by demonstrating that the protein source supports adequate growth using the PER rat bioassay described in sections 45.3.01 and 45.03.05 of the "Official Methods of Analysis of the Association of Official Analytical Chemists," 16th ed., which are incorporated by reference at § 106.160; or (iii) the scientific evidence on such infant formula otherwise demonstrates that the protein in such infant formula is of sufficient biological quality. (FDA estimates that there will be no additional PER studies required for eligible formulas because these formulas have already conducted studies meeting the requirements of § 106.96(i)(2) (Ref. 13). Furthermore, it is expected that formula manufacturers have the records of the previously conducted PER studies in their company files, and therefore no quantifiable additional cost is estimated to fulfill the records requirements for §§ 106.96(i)(4) and 106.100(q)(2) (Ref. 13).

Therefore, first year costs of § 106.96 are estimated as $2,600,045.84, the sum of the four growth studies performed on eligible infant formulas plus the estimated one growth study on an infant formula that is not an eligible infant formula, recordkeeping costs for eligible infant formulas for which no growth studies are performed, the estimated one PER study performed on an infant formula that is not an eligible infant formula, and the 34 exemptions for § 106.96(c) and 34 exemptions for § 106.96(g). The annual costs of § 106.96 are estimated to be $549,482. The interim final rule implements the statutory requirement of section 412(c)(1)(B) of the FD&C Act that infant formula manufacturers make a submission complying with section 412(d)(1) of the FD&C Act to FDA before introducing a new infant formula into interstate commerce. FDA

estimates that, for each of the four firms in the infant formula industry, one senior scientist or regulatory affairs professional will need 10 hours to gather and record information needed for infant formula submissions made under § 106.120. The annual number of submissions for a new infant formula and the number of firms that will make such submissions is not known. However, it is estimated that, annually, the industry could make submissions for 35 new infant formulas, or an average of about nine submissions per firm (Ref. 13). At a wage of $54.96 per hour ($36.64 plus 50% overhead), one submission is estimated to cost $549.60, or $54.96 hourly wage x 10 hours of work per submission = $549.60 (Ref. 16). Therefore, to comply with § 106.120, the total annual industry burden is 35 submissions x $549.60 per submission = $19,236.

Section 106.121 states that manufacturers shall submit data and information to FDA in order to provide assurances establishing that a new infant formula meets the requirements for quality factors set forth in § 106.96. FDA estimates that the cost burden of this requirement is covered by the development of a written report for a growth study required by § 106.96 because § 106.121 requires the submission of growth study data and information. Therefore, no quantifiable additional burden is estimated for § 106.121.

Table 3.--Summary of Costs Related to §106.96, §106.120, and §106.121--Assurances of quality factors in new infant formulas, new infant formula submissions, and quality factor submissions

Section	First Year Cost	Annual Cost After the First Year
§ 106.96(a) and (d), and § 106.100(p)(1)	$500,000	$500,000
§ 106.96(i)(1)(i) or § 106.96(i)(1)(ii), § 106.96(i)(4), § 106.100(p)(2)	$2,000,000	$0
§ 106.96(i)(1)(iii), § 106.96(i)(4), § 106.100(p)(2)	$50,563.20	$0
§ 106.96(f)	$1,000	$1,000
§ 106.96(g)	$11,109.84	$11,109.84
§ 106.96(c)	$37,372.80	$37,372.80
Total § 106.96	$2,600,045	$549,482

§ 106.120	$19,236	$19,236
§ 106.121	$0	$0
Total Costs Related to Quality Factors Requirements	$2,619,281.80	$568,718.64

xiv. Records (§ 106.100).

The interim final rule requires an infant formula manufacturer to prepare and maintain records that include complete information relating to the production and control of the production aggregate, including the master manufacturing order, any deviations from the master manufacturing order and any corrective actions taken because of the deviations, and the conclusions and followup of investigations of deviations (§ 106.100(e)(1), (e)(2), and (e)(4)). A manufacturer is required to maintain records pertaining to current good manufacturing practice, including records on specifications established at each point, step, or stage in the production process where control is deemed necessary to prevent adulteration (§ 106.100(e)(3)). In addition, a manufacturer must maintain other records, including the results of all testing performed on the production aggregate of infant formula (§ 106.100(e)(5)), on the distribution of the infant formula (§ 106.100(g)), and of regularly scheduled audits (§ 106.100(j)).

(Comment 10) A number of comments stated that the recordkeeping requirements would be burdensome on the infant formula industry, but provided no cost estimates of such requirements.

(Response) In the analysis of the proposed rule, total additional annual recordkeeping costs were estimated to be $450,000. FDA believes that at least 75 percent of the infant formula industry (16 of 21 plants) are currently maintaining the records that need to be kept to comply with recordkeeping requirements associated with CGMP provisions of this interim final rule (Ref. 12). FDA estimates that, for each of the estimated five plants that may not currently be

keeping records sufficient to comply with the interim final rule, the total cost to establish such records, for all CGMP provisions other than § 106.35, is $30,000 per year, per plant, or $150,000 total over the entire infant formula industry. Because other professionals with whom the Agency consulted opined that the entire infant formula industry may already be adhering to this provision (Ref. 12), this is an upper estimate, with $0 as the low estimate of cost. Full ranges are presented in the sensitivity analysis of costs related to good manufacturing practices at the end of the analysis of this option.

For the recordkeeping requirement of § 106.35(c), in accordance with § 106.100(f)(5), FDA estimates that a team of ten senior validation engineers (or other similarly skilled employees) per plant will need to work full time for the 16 weeks (640 work hours per person) to provide sufficient initial records and documentation to comply with this section. FDA estimates average compensation for a senior validation engineer to be about $46.26 per hour, including overhead (Ref. 15). The total cost for ten senior validation engineers each working 640 hours at $46.26 per hour is $296,064 per plant in the first year (10 senior validation engineers x 640 hours = 6,400, and 6,400 work hours x $46.26/hour =$296,064). However, because other professionals consulted by FDA believe that current infant formula industry systems and processes already adhere to the provisions of this section, these cost estimates will act as an upper estimate, with the lower estimate as $0.

In addition to these initial records, there are requirements for ongoing recordkeeping associated with this provision. As an upper estimate, FDA estimates that one senior validation engineer (or other similarly skilled employee) per plant will need to work 10 hours per week (520 work hours per year) to meet the ongoing recordkeeping requirements of this section. The

total cost for one senior validation engineer working 520 hours at $46.26 per hour is $24,055.20 per plant per year (520 hours x $46.26 per hour = $24,055.20). The lower estimate is $0.

Finally, an infant formula manufacturer will need to revalidate its systems when it makes changes to automatic equipment. FDA estimates that such changes are likely to occur twice a year to any aspect of a plant's system. FDA estimates that on each of the two occasions, a team of four senior validation engineers (or other similarly skilled employees) per plant will need to work full time for 4 weeks (4 weeks x 40 hours per week = 160 work hours per person) to provide sufficient revalidation of the plant's automated systems to comply with this section. The total cost for four senior validation engineers each working 160 hours twice a year ((160 hours x 2 revalidations) x 4 engineers =1,280 total work hours) at $46.26 per hour is $59,212.80 per plant (1280 work hours x $46.26 per hour = $59,212.80). However, other professionals familiar with the formula industry with whom the Agency consulted opined that current infant formula industry systems and processes adhere to this provision, so the lower cost estimate for this requirement is $0.

Table 4 summarizes the cost estimates for compliance with §106.35(c) and § 106.100(f)(5). Given that it is possible that current practices of the infant formula industry satisfy the requirements of §§ 106.35(c) and 106.100(f)(5) of the interim final rule, the total costs are presented as a function of the mean estimated number of plants that need to come into compliance (2.5 plants, rounded up to 3).

Table 4.--Mean Costs to Comply with §§ 106.35(c) and 106.100(f)(5)

	Mean Number of Plants Needing to Come into Compliance	Annual Cost per Plant to Come into Compliance	Total Mean Industry Cost
Development of Initial Validation Records	3	$296,064	$888,192

Regular Annual Recordkeeping	3	$24,055.20	$72,165.60
Semi-Annual Revalidation Recordkeeping	3	$59,212.80	$177,638.40
Total First Year Cost	3	$379,332	$1,137,996
Total Annual (beyond the first year) Ongoing Cost	3	$83,268	$249,804

Therefore, the total annual mean industry-wide cost of this provision of interim final rule with respect to CGMP requirements is $339,804 ($249,804 annually to comply with §106.35(c) and § 106.100(f)(5) + $90,000 [$30,000 x 3 plants] to comply with all other final CGMP recordkeeping requirements). Full cost ranges are presented in the sensitivity analysis of costs related to good manufacturing practices at the end of the analysis of this option.

With respect to the quality factor requirements in § 106.96 of the interim final rule, § 106.100(p)(1) and (q)(1) of the interim final rule require that, in accordance with § 106.96(d) and (h), the manufacturer of an infant formula that is not an eligible infant formula make and retain records that demonstrate that each infant formula meets the quality factors of normal physical growth and sufficient biological quality of protein. It is estimated that the burden of these recordkeeping requirements for the quality factor of normal physical growth is covered by the burden of the written growth monitoring study report or the burden of requesting an exemption from the growth monitoring study requirements in § 106.96(b) (Ref. 13). Similarly, it is estimated that the burden of these recordkeeping requirements for the quality factor of sufficient biological protein quality is covered by the burden of the written report of any necessary PER study, or the burden of requesting an exemption from the PER study requirements in § 106.96(f). Thus, § 106.100(p)(1) and (q)(1) do not represent an additional quantifiable burden to

manufacturers (Ref. 13).

Additionally, § 106.100(p)(2) and (q)(2) of the interim final rule require that, in accordance with § 106.96(i)(1) and (i)(2), the manufacturer of an infant formula that is an eligible infant formula make and retain records that demonstrate that each infant formula meets the quality factors of normal physical growth and sufficient biological quality of protein. For those eligible formulas that conduct a growth monitoring study under § 106.96(i)(1)(i) or § 106.96(i)(1)(ii), it is estimated that no additional costs will result from the recordkeeping requirements for the quality factor of normal physical growth because this requirement can be fulfilled by the written growth monitoring study report. As noted in section II.D.1.a.xiii of this document, for those eligible formulas that satisfy the quality factor of normal physical growth through compliance with § 106.96(i)(1)(iii), the cost of preparing the record required by § 106.96(i)(4) is $50,563.20. Similarly, it is estimated that for eligible formulas, there are no costs associated with complying with the recordkeeping requirements for the quality factor of sufficient biological protein quality. As noted, there is an existing requirement in current § 106.30(c)(2) to conduct a PER study, and thus, compliance with § 106.100(q)(2) of the interim final rule may be achieved by relying on the report of the study conducted under the existing requirement. Accordingly, there are no costs associated with § 106.100(q)(2) (Ref. 13).

xv. New infant formula registration (§ 106.110). Section 106.110 of the interim final rule implements section 412(c)(1) of the FD&C Act and requires the manufacturer of a new infant formula to register with FDA before the formula is shipped in interstate commerce. Based on expert opinion, all infant formula manufacturers currently register with FDA in view of the statutory requirement. Therefore, in light of current industry practice, there is no additional quantifiable burden from this provision of the interim final rule.

xvi. Infant formula submissions (§§ 106.130, 106.140, and 106.150). The submissions required by §§ 106.130 and 106.140 must be made to satisfy the requirements of section 412(d) of the FD&C Act. Similarly, the submissions required by § 106.150 must be made to satisfy the section 412(e) of the FD&C Act. Also, § 106.150 is a consolidation and recodification of current §§ 106.120 and 107.240(a) and (b). Accordingly, based on expert opinion and because these submissions are currently made as required under the FD&C Act, it is estimated that industry is already in compliance with these requirements (Ref. 13). Therefore, no costs are estimated for these sections of this interim final rule.

xvii. Administrative costs. The analysis of the 1996 proposed rule estimated that infant formula firms would incur administrative costs of $100,000 in the first year only (61 FR 36154 at 36203). No comments were received that contradicted this estimate; therefore, FDA assumes that administrative costs will be $149,000 per firm, which is $100,000 adjusted for inflation, in the first year only. Aggregated over the entire infant formula industry (four firms), the total cost for this activity is $596,000, with a lower estimate of zero.

b. Benefits of Option 1: This interim final rule. The principal benefit of this interim final rule quantified in this analysis is a decrease in the risk of illness due to Cronobacter. FDA estimates that there are, on average, four cases of illness associated with Cronobacter in the United States each year. A study of Cronobacter infections provides the data on the percentage of all cases, following the various courses of illness summarized in tables 5A and 5B (Ref. 8). Fifty-five percent of the surviving cases of acute meningitis have one or more of the following chronic effects: developmental delays, hydrocephalus, brain abscess, and reduced life expectancy. FDA bases its benefits calculations on medical costs derived from the Health Cost and Utilization Project, administered by the Agency for Healthcare Research and Quality, an

Agency within the Department of Health and Human Services (Ref. 18). Note that the courses of illness shown in table 5 are not mutually exclusive. That is, it is possible to suffer from more than one condition shown in the table. Therefore, the percent of all cases sums to more than 100 percent.

Table 5A.--Primary Health Effects of Various Courses of Illness Associated With Cronobacter

Course of Illness	Death	Bacteremia	Acute Meningitis
Percent of All Cases	33%	22.6%	67.7%
Duration		12 days	41 days
EQ-5D Rating		33322 (.118)	33322(.118)
Quality-Adjusted Life Days (QALDs) lost/day of illness		.752	.752
QALD lost/illness (Duration * QALD lost/day		9.024	30.46
Value of lost QALDs, at $586/day (discounted at 3%)		$5,288	$17,847
Medical Cost of Treatment		$26,214	$58,059
Total Cost per Course of Illness (Value of lost QALD's + medical cost)	$7,900,000	$31,502	$75,906

Table 5B.--Secondary Effects of Meningitis*

Secondary Effect	Brain Abscess	Developmental Delay	Hydrocephalus	Decreased Life Expectancy
Duration	18 days	9,534 days	11 days	5,776 days
EQ-5D Rating	33322 (.118)	22221-33322 (.118 - .689)	33322 (.118)	
QALD lost/day of illness	.752	.47 (average)	.752	.403**
QALD lost/illness (duration * QALD lost/day)	18	4447.38	7.90	2330.41
Value of lost QALDs, at $586/day (discounted at 3%)	$7,712	$2,606,163	$4,627	$1,365,623
Medical Cost of Treatment	$131,095	$55,911	$62,119	n/a
Total Cost per Course of Illness	$138,807	$2,662,074	$66,746	$1,365,623

*Approximately 55% of cases of Cronobacter have secondary illnesses, and this percentage will be used for the purposes of calculating the weighted average cost of secondary illnesses.
**This is the QALD value of health lost every day of the length of time life is reduced, or .87 - .47 = 40.

Estimating benefits from this interim final rule involves the use of quality-adjusted life years (QALYs). QALYs can be used to measure the loss of well-being that an individual suffers due to a disease or condition. As QALYs are only a measure of a loss of well-being, cost of illness is estimated separately. QALYs range from 0 to 1, where 0 is equivalent to death and 1 is equivalent to perfect health for 1 year. In this analysis, the QALY of starting health is valued at .87 (Ref. 19).

In this analysis, for both acute and secondary complications from Cronobacter, the EQ-5D health index adjusted for U.S. health status preference weights is used to calculate QALD value. The EQ-5D is a health-related quality of life measure that generates a five-digit composite score or index reflecting the value associated with a given health state (Ref. 20). The EQ-5D index permits an estimate of an individual's disutility from being ill due to a food-related illness in terms of the number of QALDs lost due to that illness. The EQ-5D scale consists of five domains that assess an individual's mobility, ability to perform self-care activities, ability to

perform usual activities (such as going to work or school), level of pain and discomfort, and level of anxiety and depression as a result of their medical condition. This index translates to a decimal that is then used to calculate QALDs lost per illness. For example, as shown in table 5A, the EQ-5D rating for acute meningitis is 33322, and a decimal score of .248. This means that current health is now .248. The decimal value of lost health is then .87 - .248 = .752.

Multiplying the decimal value of lost health by the duration of illness yields an estimate of lost QALDs. In this analysis, QALDs are valued by multiplying the number of QALDs lost by $586, based on $7.9 million for a value of statistical life and $214,000 for the value of a QALY. The values of a statistical life year and statistical life are central estimates here. In the Analysis of Uncertainty, benefits are also calculated using low and high estimates of the values of statistical life and life year.

Multiplying the total cost per course of illness by the percentage of all cases that end with that course of illness gives a weighted average cost per case of Cronobacter. There are two components to the average weighted cost: the costs associated with the primary effects (death, bacteremia, and meningitis) and the costs associated with the secondary complications associated with Cronobacter (Ref. 8): hydrocephalus, brain abscess, developmental delays, and decreased life expectancy. Again, using the data in table 5A, the weighted average cost of primary illness per case of Cronobacter is calculated by multiplying the total cost per course of illness (for example, $75,906 for acute meningitis) by the percentage of all cases of illness that a specific illness represents (for example, 68% for acute meningitis), then adding these together. Therefore, for Cronobacter, the weighted average cost is about $2.7 million dollars (.677 x $75,906 [for acute meningitis] + .226 x $31,502 [for bacteremia] + .33 x $7,900,000 [for death]). Using the data in table 5B and the same method of calculation used for the primary illness (and

noting that about 55% of cases of Cronobacter have secondary illness), the weighted average cost of secondary complications is about $2.3 million ($66,746 x .5543 [for hydrocephalus] + $138,807 x .5543 [for brain abscess] + $2,662,074 x .5543 [for developmental delay] + $1,365,623 x .5543 [decreased life expectancy]). The total weighted average cost of a case of Cronobacter is thus about $5 million ($2.7 million for weighted average cost of primary courses of illness + $2.3 million for weighted average cost of secondary courses of illness) and for the estimated four cases per year of Cronobacter the total potential annual benefit of eliminating the Cronobacter hazard in infant formula is about $20 million (4 x $5 million). The estimated four cases per year of Cronobacter associated with infant formula and the apparent increase in the number of cases over the last decade indicate that the infant formula industry's current voluntary activities may not be sufficient to provide the protection necessary to help ensure the safety of the sole source of nutrition for infants. The provisions of the interim final rule will address the weaknesses in formula production that may result in the contamination of infant formula with Cronobacter and lead to these types of illnesses and deaths.

The other primary benefit of this rule is preventing nutritional deficiencies. Hypochloremic metabolic alkalosis, a syndrome associated with chloride deficiency, was diagnosed in 141 infants who consumed chloride-deficient soy formulas in the late 1970's. As noted, symptoms of metabolic alkalosis are irritability, rapid heart rate, irregular heartbeat, and a drop in blood pressure. If severe cases are left untreated, convulsions, heart failure, and coma may result. It is not possible to predict future nutritional deficiencies resulting from an improperly formulated infant formula or the consequences of such deficiencies. However, nutritional deficiencies in infants can develop quickly and can result in irreversible neurological damage and even death.

Even without severe illness or death, nutritional deficiencies can contribute to milder conditions which can have long-term negative consequences for children. As described in Malloy, et al. (Ref. 1), previous studies suggest that some children with documented hypochloremic metabolic alkalosis suffered developmental delays, and the authors performed a follow-up study on a subset of children who suffered from hypochloremic metabolic alkalosis as a result of being fed the chloride-deficient soy formula. These children were compared to a control group of children who were fed the same formula but did not have documented hypochloremic metabolic alkalosis. While the authors found that the children with the illness recovered from their initial growth failure, they also found that these children are at risk for deficits in language skills.

Such language skill deficits may result in losses in earnings over an individual's working life. Dickinson and Verbeek (Ref. 21) estimate that learning disabilities could contribute, after adjusting for individual characteristics, to a wage differential of $1.00 per hour, or $2,000 per year, based on 50 weeks of work at 40 hours per week (50 weeks x 40 hours per week = 2,000 hours and 2,000 hours x $1 = $2,000).

If this interim final rule had been in place in 1978, the quality factor requirements and the requirements for nutrient testing would have provided additional safeguards to prevent hypochloremic metabolic alkalosis that occurred in 141 children as a result of consumption of chloride deficient infant formula. If all 141 children were later affected by language deficits that decreased lifetime earnings, the value of the lost earnings would have resulted in a total of $282,000 a year (141 children x $2,000/year = $282,000). Over a 30-year working life span, this loss is equivalent to about $5.5 million discounted at 3 percent or about $3.5 million when discounted at 7 percent.

In addition, problems are associated with other nutrient deficiencies. While it is not possible to quantify benefits from testing for these nutrients, they are worth noting qualitatively. For example, Hatun, et al. (Ref. 22) state that vitamin D deficiency or nutritional rickets can develop very early in infancy and is usually characterized by severe hypocalcemic symptoms. The authors recommend vitamin D supplementation of all infants, beginning during the first days of life. Darnton-Hill, et al. (Ref. 23) point out that iodine deficiency in pregnancy is causing as many as 20 million infants per year to be born mentally impaired. This has been estimated to lower the average IQ of those born in iodine deficient areas by 10-15 IQ points, which subsequently adversely affects school performance, decreases productivity, and results in an enormous economic burden. Graham, et al. (Ref. 24) examined vitamin B-12 deficiency in newborns. They find that vitamin B-12 deficiency in infants is associated with marked developmental regression and poor brain growth. Again, it is not possible to quantify benefits from testing for these nutrients, but these examples underscore the need for nutrient testing of infant formula.

c. Summary of costs and benefits of the interim final rule.

Table 6 summarizes the costs of the interim final rule by provision. As with table 2, estimates of the good manufacturing practice provisions of this interim final rule are presented as means, due to the possibility that the infant formula industry already may be adhering to those provisions. Costs related to § 106.96 and recordkeeping related to quality factors are presented as full cost estimates. Furthermore, these cost estimates may be overstated if the one firm in the infant formula industry does not sell formula in domestic commerce and exports infant formula in a manner that is consistent with applicable requirements under sections 412 and 801 of the

FD&C Act. Full ranges of costs related only to good manufacturing practices are presented in the sensitivity analysis at the end of this option.

Table 6.--Summary of Mean Costs and Mean Benefits of This Interim Final Rule

Provisions Related to Good Manufacturing Practices	First Year	Annual After the First Year
§ 106.20--Controls to prevent adulteration caused by facilities	$15,625	$15,625
§ 106.30--Controls to prevent adulteration caused by equipment or utensils	$3,100,000	$3,100,000
§ 106.60--Controls to Prevent Adulteration During Packaging and Labeling of Infant Formula	$39	$39
§ 106.91--General quality control	$31,000	$31,000
§106.94--Audit plans and procedures	$925	$925
§ 106.100--Records pertaining to CGMP provisions	$1,227,996	$339,804
Administrative costs	$298,000	$0
Total Mean CGMP Provision Costs	$4,673,585	$3,487,393
Provisions Related to Quality Factors	First Year	Annual After the First Year
§§ 106.96, 106.120, and 106.121--Assurances of quality factors in new infant formulas, new infant formula submissions, and quality factor submissions	$2,619,282	$568,719
Total Costs[1]	$7,292,867	$4,056,112
Mean quantified benefits[2]	$10,000,000	$10,000,000

[1]Annualized first year mean costs are $1,170,551 discounted at a rate of 3% over 7 years.
[2]Mean quantified benefits represent a range of benefits from $0 to $20 million.

Net quantified benefits are estimated to be about $2.70 million in the first year and about $6 million annually thereafter. The present value of annual net benefits is about $74 million or $116.54 million, given a 7 percent or 3 percent discount rate over 30 years. If this rule prevents nutritional deficiencies, then net benefits will be larger, as illustrated by the benefits of preventing human capital losses associated with developmental deficiencies for the 141 children with documented hypochloremic metabolic alkalosis in 1978 (Ref. 21). As presented in the

discussion of benefits, preventing those effects would have resulted in benefits of about $5.5 million or $3.5 million, discounted at 3 percent or 7 percent.

Analysis of Uncertainty

As stated elsewhere in this analysis, given that certain professionals knowledgeable about the infant formula industry with whom the Agency consulted have stated that they believe that the current industry processes and systems adhere to the good manufacturing provisions in the interim final rule, it is possible that total costs of the interim final rule for compliance with good manufacturing practice provisions are zero. However, to the extent that the infant formula industry already adheres to these provisions, benefits are also minimized. Also, it is possible that some cases of Cronobacter may be a result of the environmental presence of the organism (for example, in the home) rather than contaminated infant formula. To the extent that contamination comes from the environment rather than contaminated infant formula, benefits will be less than what are estimated here. However, for the purposes of estimating benefits for this interim final rule, it is not possible to distinguish between environmental contamination and contamination from infant formula.

While tables 3 and 6 present costs of CGMP provisions and benefits as means based on a range of estimates, table 7 presents the full ranges of costs for CGMP provisions and the full range of benefits estimated for this rule. Table 7 presents the results of a simple Monte Carlo simulation of uncertainty for the eventual annual costs of the CGMP provisions of this rule. Because there is less uncertainty regarding whether industry is adhering to the quality factor provisions outlined in § 106.96, estimated costs attributable to these requirements are not included here. Furthermore, this uncertainty analysis includes a Monte Carlo analysis of benefits, due to the estimation that quantifiable benefits will be related to CGMP provisions of

the rule and not quality factor requirements. Results are reported for the 5th and 95th percentiles, as well as for the mean value. Based on the data for which the Agency has been able to characterize uncertainty, FDA believes that the eventual annual cost of CGMP provisions of this interim final rule could range between $0 and $6.6 million. This range is a result of the lack of certainty regarding the extent to which the infant formula industry is already voluntarily engaged in activities that adhere to the CGMP provisions in the interim final rule. Table 8 presents an uncertainty analysis of the benefits of the interim final rule. Depending on the value of statistical life used, benefits could range from $0 to $25.7 million.

Costs

Table 7.--Summary of Costs Related to CGMP Provisions of This Interim Final Rule: Analysis of Uncertainty

Provision	Cost if Industry is Already in Compliance	5th Percentile	Mean Estimated Annual Cost	95th Percentile	Maximum Estimated Cost of Compliance
§ 106.20--Controls to prevent adulteration caused by facilities--Radiological Testing	$0	$261	$2,625	$4,987	$5,250
§ 106.20--Controls to prevent adulteration by facilities--Bacteriological Testing	$0	$1,295	$13,000	$24,700	$26,000
§ 106.30--Controls to prevent adulteration caused by equipment or utensils	$0	$309,607	$3,100,000	$5,889,654	$6,200,000
§106.60--Controls to prevent adulteration during packaging and labeling of infant formula	$0	$3.93	$39	$74.78	$78.72
§106.91--General quality control	$0	$3,096	$31,000	$58,896	$62,000
§106.94--Audit plans and procedures	$0	$92.39	$925	$1,757	$1,850
§106.100--Records related to CGMP provisions	$0	$28,255	$283,131[1]	$538,009	$566,340
Total costs	$0	$342,610	$3,430,720	$6,518,078	$6,861,519

[1] In section II.D.1.a.xiv of this document, this amount is presented as $339,804 due to rounding the mean number of plants from 2.5 to 3.

Table 8.--Summary Estimated Benefits from Averted Illnesses Caused by Cronobacter: Analysis of Uncertainty

Estimated Benefits from Averted Illnesses if Industry is Currently in Compliance	5th Percentile	Mean	95th Percentile	Benefits from Averted Illnesses if Industry is Not Currently in Compliance
If VSLY = $214,000, and VSL=$7,900,000				
0	$997,330	$10 million	$19 million	$20 million
If VSLY=$107,000 and VSL=$1,200,000				
0	$558,401	$5.6 million	$10.6 million	$11.2 million
If VSLY=$322,000 and VSL=$12,200,000				
0	$1.3 million	$12.9 million	$24.4 million	$25.7 million

2. Option 2: Finalize the Proposed Rule

The proposed rule, if finalized, would have been more restrictive than the interim final rule in several ways. In this interim final rule, FDA has not prescribed or limited the ways in which many of the required results may be achieved as long as infant formulas are manufactured in a manner that is designed to prevent adulteration of the formula. The following is a subset of the ways that the interim final rule has been made less restrictive.

- Manufacturers will not be required to test for L. monocytogenes, B. cereus, E. coli, or S. aureus, saving at least $100 per production aggregate lot for manufacturers that are not currently conducting this testing.
- Cold storage facilities may not need to be operated continuously at a temperature as low as 40°F; facilities may be operated up to 45°F provided the manufacturer has scientific data and information to demonstrate that certain criteria are met, which may

eliminate the need to replace existing refrigeration units and to incur costs associated with operating at the lower temperature.

- Manufacturers may validate their systems using the first production aggregate of a regular production run, rather than use a separate production aggregate that is not part of a regular production run, provided that the validation is completed prior to release of the formula, which eliminates the need for a separate validation production aggregate.
- Formula that does not meet production specifications is not automatically considered adulterated but may be evaluated to determine whether adulteration has occurred, which may eliminate unnecessary waste or reprocessing of safe product.
- Manufacturers may choose to reject product or materials rather than be required to retest and reexamine them, which will permit speedier resolution of problems.
- Periodic testing requirements have been reduced, which simplifies the requirement and results in less duplication of testing.
- Stability testing requirements have been revised to allow flexibility for nutrients that are known to be more stable, which reduces the amount of necessary testing.
- Raw materials, in-process materials, and finished product may be separated by means other than physical separation, which reduces the need for expensive changes to the existing physical plant.

FDA has not estimated the total cost of these provisions of the proposal. However, because manufacturers will not be required to test for L. monocytogenes, B. cereus, E. coli, or S. aureus, it is assumed that the firms in the infant formula industry that are conducting such testing will save at least $100 per production aggregate, or a total of $520,000 per production aggregate.

This assumes testing one production aggregate per day per processing line, 20 total industry processing lines, and 260 processing days per year. Furthermore, FDA believes that the more restrictive proposed rule would not have been more protective of infants than the interim final rule.

3. Option 3: Require Only End product Testing for Pathogens (§ 106.55) and Nutrient Testing and Stability Testing (§ 106.91) and Quality Factor Requirements for Non-Exempt Infant Formulas (§§ 106.96, 106.120, and 106.121)

As an alternative approach, FDA could require only the provisions in §§ 106.55, 106.91, 106.96, 106.120, and 106.121. This would substantially reduce the costs of the interim final rule but would fail to implement all of the provisions under section 412 of the FD&C Act and would fail to address all of the requirements the Agency has determined to be necessary to prevent adulteration of infant formula, including those related to CGMP and other provisions in section 412 of the FD&C Act. The estimated costs of this option are $568,719 annually ($0 for nutrient testing and stability testing[2] + $568,719 for quality factor requirements). Chemical testing for nutrients identifies the nutrient content of an infant formula but cannot be used to determine whether the nutrients in the formula will be biologically available in an appropriate form for digestion, absorption, and utilization by an infant (i.e., bioavailable). Bioavailability is a vital component of safety, and chemical testing alone cannot provide assurance of the nutritional adequacy of an infant formula. The consequences of the omission of any essential nutrient or its lack of biological availability in an infant formula could result in severe consequences (including irreversible neurological damage or death) to an infant. The potential benefits of this option would only be the benefits of preventing some nutritional deficiencies. FDA is not able to

[2] It is estimated earlier that industry is already in compliance with the requirements of § 106.55.

calculate these benefits on an annual basis. However, as an illustration, preventing human capital losses associated with developmental deficiencies for the 141 children with documented hypochloremic metabolic alkalosis in 1978 would have resulted in benefits of about $5.5 million (discounted at 3 percent) or $3.5 million (discounted at 7 percent).

Although testing is important in ensuring the safety of products, FDA does believe that infant formula manufacturers already conduct end product testing for pathogens, nutrient testing, and stability testing, and conduct a growth monitoring study for certain infant formulas. Testing is not a perfect means of ensuring the safety and bioavailability of infant formula. For example, cases of Cronobacter persist in spite of industry testing of finished formula, which could be due to contamination during processing that is not detected with such testing. Also, sampling and analysis alone are very inefficient means of controlling very rare but very severe hazards.

Option 3 would not sufficiently address a significant, persistent, identified hazard associated with powdered infant formula. Therefore, the Agency is not relying solely on testing and growth monitoring studies to ensure the safety of infant formula, the sole source of nutrition for infants. The additional provisions for sanitation, quality control, and recordkeeping required by the interim final rule, for example, are important to ensure the safety of formula, and these requirements provide the additional safeguards that will reduce the risk of illness from infant formula.

4. Option 4: Require the Provisions of This Interim Final Rule, Except a Growth Monitoring Study as Assurance for the Quality Factor of Normal Physical Growth

This interim final rule requires that a manufacturer conduct a growth monitoring study for certain infant formulas (§ 106.96(b)). Under this option, the estimated costs would be reduced by up to $500,000 per year from those estimated for the interim final rule, and potential

benefits would be reduced by the amount of the human capital losses estimated as a result of nutritional deficiencies, or about $3.5 million (discounted at 7 percent) or $5.5 million (discounted 3 percent). By removing this section from the interim final rule, the rule would fail to address one of the primary reasons that Congress passed the Infant Formula Act, that is, to ensure that infant formula supports normal physical growth of infants. Chemical analysis of nutrient content cannot be used to predict whether an infant fed an infant formula will grow normally. In contrast, a growth monitoring study may be used to demonstrate that the chemically tested formula has nutrients in a form that are available to the infant in amounts that support normal physical growth in a volume of formula that is reasonable for an infant to consume.

III. Regulatory Flexibility Analysis for Interim Final Rule

FDA has examined the economic implications of this interim final rule as required by the Regulatory Flexibility Act, 5 U.S.C. 601-612. If a rule has a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would lessen the economic effect of the rule on small entities. The Agency finds that this interim final rule will not have a significant economic impact on a substantial number of small entities.

. IV. Paperwork Reduction Act of 1995

This interim final rule contains information collection requirements that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520) (the PRA). The title, description, and respondent description of the information collection requirements are given in the following paragraphs, including estimates of the one-time burden of developing an audit plan and audit procedures, developing production

and in-process control systems, audit plans, one time growth studies and petitions submitted to the Agency for eligible infant formulas. Annual burdens of batch production and control records, records pertaining to the distribution of infant formula, records pertaining to regularly scheduled audits, quality factor requirements, and registration and submission requirements are also estimated. Included in the burden estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

In the July 9, 1996, proposed rule, FDA included an analysis of the information collection provisions of the proposal under the PRA and requested comments on four questions relevant to that analysis (61 FR at 36205-36206). Subsequently, in 2003, the Agency reopened the comment period to update comments and to receive any new information on all issues, including on the PRA analysis (68 FR 22341). In response to these requests, FDA received no comments specifically referring to the Agency's 1996 PRA analysis or otherwise referring to the PRA. FDA did receive comments on the substantive provisions of the proposed rule, including comments on the proposed recordkeeping and other provisions of the proposal that would result in information collections. FDA has summarized and responded to these comments in this document .

As noted, the 1996 proposal included a PRA analysis. FDA is re-estimating the burden of this interim final rule using current burden analysis methodology. The Agency invites comments on new issues relating to the following topics: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions

used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Revision of OMB Control No. 0910-0256 by the Interim Final Rule

These estimated annual recordkeeping burdens have changed from the burdens estimated for the OMB control number 0910-0256 (75 FR 67983; November 4, 2010). The estimated recurring burden for § 106.100 has decreased from 20,000 hours estimated in OMB Control No. 0910-0256 to 11,595.65 hours due to a revised estimate of the industry's current recordkeeping practices. In this interim final rule, current § 106.120 is consolidated with current § 107.240 and recodified as § 106.150 in the interim final rule.

Title: Current Good Manufacturing Practice, Quality Control Procedures, Quality Factors, Notification Requirements, and Records and Reports, for the Production of Infant Formula Under 21 CFR Parts 106 and 107.

Description: This new collection of information will be performed by manufacturers of infant formula. The records requirements of this interim final rule include records pertaining to: (1) Production aggregate production and control; (2) growth studies and Protein Efficiency Ratio (PER) studies; (3) current good manufacturing practice and quality control; (4) distribution of infant formula; and (5) regularly scheduled audits, including audit plans and procedures. In addition, this interim final rule includes reporting requirements pertaining to: (1) Registration of new infant formula; (2) submission requirements for new infant formulas; (3) submissions before the first production and introduction into interstate commerce to verify that the formula complies with the requirements of the FD&C Act; (4) submission requirements when there is a change in

the formulation or processing of the formula that may affect whether the formula is adulterated; and (5) voluntary petition relating to eligible infant formulas.

FDA has concluded that recordkeeping and reporting are necessary for the success of the current good manufacturing practice and quality control procedures (including production aggregate control and distribution), quality factors, audits, and registration and notification requirements. Records of actions taken due to each requirement are essential for manufacturers to implement this rule effectively. Further, records and reports are essential for FDA to be able to determine whether a firm is in compliance with the rule.

Analysis of Burden Estimates Resulting from this Interim Final Rule

Description of Respondents: Infant Formula Manufacturers

FDA estimates the burden of this collection of information as follows:

The total one-time estimated burden imposed by this collection of information is 35,630 hours. The total annual estimated burden imposed by this collection of information is 12,680.85 (11,225.35 recordkeeping hours + 1, 455.5) hours. There are no capital costs or operating and maintenance costs associated with this collection of information. The estimated burden for this interim final rule is based on "Evaluation of Recordkeeping Costs for Food Manufacturers," Eastern Research Group Task Order No. 5, Contract No. 223-01-2461. FDA estimates that firms will be able to fulfill recordkeeping requirements with existing record systems; that is, FDA estimates that it will not be necessary for infant formula firms to invest in new recordkeeping systems.

For records relating to CGMP requirements, the number of record keepers in column 2 of table 9 and table 10 is based on the Agency's expert estimation of the number of plants that may not already be adhering to the recordkeeping provisions of this interim final rule. The RIA

estimated that 25 percent of all infant formula plants were not currently adhering to the CGMP provisions under § 106.100 (5 out of 21 plants) and, unless otherwise specified, burdens are estimated based on these five plants. Furthermore, the Agency estimates that plants will collect the same information across the various infant formulas produced by each firm. For records relating to quality factor requirements, the number of record keepers in column 2 of table 9 and table 10 varies according to the nature of the requirement and other factors identified in the discussion that follows.

The one-time burdens result from the need to develop production and in-process control systems, validation records, one time growth studies, and petitions submitted to the Agency for eligible infant formulas, and are presented in table 9. Development of in-process control systems and audit plans will both likely occur on the plant level. Petitions regarding eligible infant formulas will be developed per formulation. It is possible that one or more manufacturers of an eligible infant formula will choose to conduct a growth study of an infant formula formulation, and the information collection and recordkeeping for such studies, as well as any petitions developed for these eligible infant formulas, will also represent one-time burdens.[3]

For records pertaining to production and in-process controls, FDA estimates that, at most, five plants will be required to develop production records to comply with § 106.6(c)(5), and § 106.100(e)(1) and (e)(3) (Ref. 12). A team of two senior validation engineers (or other similarly skilled employees) per plant (2 x 5 plants = 10 workers) will each need to work 20 hours to provide sufficient initial baseline records and documentation to develop records pertaining to production and in-process controls in order to comply with § 106.6(c)(5) and § 106.100(e)(1) of the interim final rule, for an industry total of 200 hours (2 workers x 5 plants x 20 hours = 200

[3] Hourly burdens for infant formulas that are not eligible infant formulas are estimated on an annual basis.

hours), as presented in line 1 of table 9.

For the recordkeeping requirement of § 106.35(c), in accordance with § 106.100(f)(5), FDA estimates that a team of ten senior validation engineers (or other similarly skilled employees) per plant will need to work full time for the 16 weeks (640 work hours per person) to provide sufficient initial records and documentation to comply with this section. The total burden for ten senior validation engineers each working 640 hours is 6,400 per plant in the first year (10 senior validation engineers x 640 hours = 6,400). For five plants, the total one time hourly burden is 5 plants x 6,400 hours = 32,000 hours, as presented in line 2 of table 9.

Section 106.96(i) of the interim final rule outlines certain requirements for eligible infant formulas; these include the requirement that such infant formulas meet the quality factor of normal physical growth. It is estimated that among all eligible infant formulas, there are 50 formulations currently on the market that must satisfy the quality factor of normal physical growth (Ref. 13). It is likely that some eligible infant formulas will be the subject of a growth monitoring study; it is estimated that, for eligible infant formulas, industry will perform four growth studies one time as a result of the requirement of § 106.96(i)(1) (Ref. 13). It is assumed that the balance of the 50 eligible infant formulations (46 formulations) will comply with § 106.96(i)(1)(iii) by assembling from existing studies, data, and information a record that demonstrates that the formulation supports normal physical growth.

It is estimated that the data collection associated with a growth study performed to comply with § 106.96(i)(1) will be assembled into a written study report and that the study report will be kept as a record in compliance with § 106.96(i)(1)(i) or § 106.96(i)(1)(ii), § 106.96(i)(4), and § 106.100(p)(2). As noted, four growth studies of eligible infant formulas are estimated as a result of this interim final rule. Therefore, it is estimated that four growth study reports will be

generated as a result of this interim final rule. It is estimated that one report will require one senior scientist to work 16 hours to compile these data into a comprehensive report. Therefore, four growth study reports x 16 hours = 64 hours for compliance with § 106.96(i)(1)(i) or § 106.96(i)(1)(ii), as presented in line 3 of table 9. Once prepared, the maintenance of the growth study report will also fulfill the requirements of §§ 106.96(i)(4) and 106.100(p)(2) without any additional quantifiable hourly burden.

The estimates for the information collection burden assume that the growth studies for eligible formulas will be conducted consistent with the requirements of § 106.96(b) of the interim final rule. The interim final rule (§ 106.96(b)(2)) requires that several pieces of data be collected and maintained for each infant at six visits during each such study. The burden estimates for these specific collections, as applied to eligible infant formulas, are discussed below.

A study conducted according to the requirements of § 106.96(b)(2) must include the collection of anthropometric measurements of physical growth and formula intake, and § 106.96(b)(3) requires that the anthropometric measurements be taken six times during the growth study. It is estimated that in a growth study of 112 infants, two nurses or other health professionals with similar experience will need 15 minutes each per infant at each of the required six times to collect and record the required anthropometric measurements. Therefore, 2 nurses x .25 hours = .5 hour per infant, per visit, and .5 hour x 6 visits = 3 hours per infant. For 112 infants in a study, 3 hours x 112 infants = 336 hours to collect anthropometric information for one growth study. For four growth studies, this burden is 1,344 hours (336 hours x 4 studies), as presented in line 4 of table 9. In addition, it is estimated that one nurse will need 15 minutes per infant to collect and record the formula intake information. That is, .25 hour x 6 visits = 1.5 hour

per infant, and 1.5 hour per infant x 112 infants = 168 hours to collect information on formula intake for one growth study. For four growth studies, this burden is 672 hours (168 hours x 4 studies), as presented in line 5 of table 9.

Section 106.96(b)(4) requires plotting each infant's anthropometric measurements on the 2009 CDC growth charts. This task is estimated to take five minutes per infant at each study visit. Therefore, six data plots x 112 infants = 672 total data plots, and 672 data plots x .08 hour per comparison = 53.75 total hours. For four growth studies, this burden is 215 hours (53.75 hours x 4 studies), as presented in line 6 of table 9.

Finally, § 106.96(b)(5) requires that data on formula intake by the test group be compared to that of the concurrent control group. FDA estimates that one nurse or other health care professional with similar experience will need five minutes per infant, for each of the six study visits, to fulfill the requirements of this section. Therefore, six comparisons of data x 112 infants = 672 data comparisons, and 672 data comparisons x .08 hour per comparison = 53.75 total hours. For four growth studies, this burden is 215 hours (53.75 hours x 4 studies), as presented in line 7 of table 9.

Section 106.100(p)(2) and (q)(2) require that, in accordance with § 106.96(i)(4), a manufacturer keep records demonstrating that an eligible infant formula fulfills one or more of the criteria listed in § 106.96(i)(1) and one or more of the criteria in § 106.96(i)(2). It is estimated that, for an eligible infant formula for which a growth study is performed, the records required by § 106.100(p)(2) are fulfilled by the growth study data collection and the study report and do not represent an additional quantifiable hourly burden to these manufacturers (Ref. 13). In addition, it is estimated that the records required by § 106.100(q)(2) are fulfilled by an infant formula firm by virtue of the current requirement in § 106.30(c)(2) to conduct a PER study, and

thus, this requirement does not represent an additional quantifiable hourly burden (Ref. 13). For an eligible infant formula for which no growth study is performed, the recordkeeping burden of § 106.100(p)(2) is estimated to be 20 hours per record for each of 46 estimated formulations due to the need for manufacturers to compile existing data into a record. Therefore, 20 hours x 46 formulations = 920 hours for this subset of manufacturers to comply with § 106.100(p)(2), as presented in line 8 of table 9. This 920 hours represents the total industry burden for compliance with § 106.100(p)(2). This burden is estimated also to cover the requirements of § 106.96(i)(1)(iii), which state that an eligible infant formula meets the quality factor of normal physical growth if the scientific evidence on such infant formula otherwise demonstrates that such formula supports normal physical growth.

Section 106.96(i)(3), which establishes a voluntary petition process for eligible infant formulas, is estimated to be a one-time burden. Under § 106.96(i)(3), the manufacturer of an eligible infant formula may submit a citizen petition in accordance with 21 CFR 10.30 that demonstrates that such formula meets the quality factor of normal physical growth, demonstrates that such formula meets the quality factor of sufficient biological quality of the protein, or both. Each petition may address both quality factors but may only address one infant formula formulation. It is estimated that one petition will be submitted for each eligible infant formula formulation, including the four eligible infant formulas formulations for which growth studies are performed (Ref. 13). Section 106.96(i)(3) of the interim final rule refers to previously approved collections of information found in FDA regulations. These collections of information are subject to review by OMB under the PRA. The collections of information in § 10.30 have been approved under OMB control number 0910-0183 (General Administrative Procedures: Citizen Petitions; Petition for Reconsideration or Stay of Action; Advisory Opinions).

Accordingly, as shown in table 9, FDA estimates a total first year only hourly burden of 35,630 hours.

Section 106.20(f)(3) requires that manufacturers conduct water testing at least annually for chemical contaminants, every 4 years for radiological contaminants, and weekly for bacteriological contaminants. FDA estimates that it is part of normal business practice for infant formula plants to test for chemical contaminants and keep records of those tests on a regular basis; therefore, this requirement is not a new collection of information (Ref. 12).

However, it is estimated that the requirement to test at least every 4 years for radiological contaminants will represent a new collection of information for 21 infant formula plants (Ref. 12). In addition, it is estimated that collecting water for all testing in § 106.20(f)(3) takes between 1 and 2 hours (Ref. 12). For the purposes of this analysis, it is conservatively estimated that water collection takes, on average 1.5 hours and that water collection occurs separately for each type of testing. It is estimated that performing the test (collecting the information) will take 1.5 hours per test, every 4 years. Therefore, 1.5 hours per plant x 21 plants = 31.5 total hours, every 4 years, as seen in line 9 of table 7. Furthermore, § 106.20(f)(4) and § 106.100(f)(1) require firms to make and retain records of the frequency and results of water testing. For the 21 plants that are estimated not to currently test for radiological contaminants, this burden is estimated to be 5 minutes per record every 4 years. Therefore, 0.08 hour per record x 21 plants = 1.68 hours, every 4 years for the maintenance of records of radiological testing, as seen on line 10 of table 9.

It is estimated that the requirement to test weekly for bacteriological contaminants is a new burden for five infant formula plants. It is estimated that performing the test (collecting the information) will take 5 minutes per test once a week. Annually, this burden is 0.08 hours x 52

weeks = 4.16 hours per year, per plant, and 4.16 hours per plant x 5 plants = 20.8 total annual hours, as seen on line 11 of table 9. Furthermore, for the five plants that are estimated to not currently test weekly for bacteriological contaminants, this burden is estimated to be 5 minutes per record, every week. Therefore, 0.08 hour per record x 52 weeks = 4.16 hours per plant for the maintenance of records of bacteriological testing. Accordingly, 4.16 hours x 5 plants = 20.8 annual hours, as seen on line 12 of table 9.

The interim final rule requires that certain instruments be calibrated against a known reference standard, and that records of these calibration activities be made and retained (§§ 106.30(d) and 100.100(f)(2)); these records will be kept at the plant level. FDA estimates that one senior validation engineer (or other similarly skilled employee) for each of the five (at most) plants will need to spend about 13 minutes per week to satisfy the ongoing calibration recordkeeping requirements of §§ 106.30(d) and 100.100(f)(2). Therefore, 5 recordkeepers x 52 weeks = 260 records; 260 records x .21 hour per record = 55 hours as the total industry annual burden, as presented in line 13 of table 9.

The interim final rule (§§ 106.30(e)(3)(iii) and 106.100(f)(3)) requires the making and retaining records of the temperatures of each cold storage compartment. Based on expert opinion, FDA estimates that five (at most) plants are not currently adhering to this recordkeeping provision, and that at each of these five plants, compliance will require one senior validation engineer (or other similarly skilled employee) about 13 minutes per week. Therefore, 5 recordkeepers x 52 weeks = 260 records; 260 records x .21 hours per record = 55 hours as the total industry annual burden, as presented in line 14 of table 9.

The interim final rule (§§ 106.30(f) and 100.100(f)(4)) requires the making and retention of records of ongoing sanitation efforts. Based on expert opinion, FDA estimates that five (at

most) plants are not currently adhering to this recordkeeping provision, and that at each of these five plants, compliance will require one senior validation engineer (or other similarly skilled employee) about 12 minutes per week. Therefore, 5 recordkeepers x 52 weeks = 260 records; 260 records x .19 hours per record = 49.4 hours as the total industry annual burden, as presented in line 15 of table 9.

There will be annual recordkeeping associated with §§ 106.35(c) and 106.100(f)(5). It is estimated that one senior validation engineer (or other similarly skilled employee) per plant will need to work 10 hours per week (520 work hours per year) to meet the ongoing recordkeeping requirements of this section. For the estimated five (at most) plants not adhering to the recordkeeping provisions of § 106.35, the total annual burden for this provision is 520 hours per plant x 5 plants = 2,600 annual hours, as shown in line 16 of table 9. In addition, an infant formula manufacturer will need to revalidate its systems when it makes changes to automatic equipment. FDA estimates that such changes are likely to occur twice a year to any aspect of the plant's system, and that on each of the two occasions, a team of four senior validation engineers (or other similarly skilled employees) per plant will need to work full time for 4 weeks (4 weeks x 40 hours per week = 160 work hours per person) to provide revalidation of the plant's automated systems sufficient to comply with this section. The total annual burden for four senior validation engineers each working 160 hours twice a year is 1,280 hours ((160 hours x 2 revalidations) x 4 engineers =1,280 total work hours), per plant. Therefore, 1,280 hours per plant x 5 plants = 6,400 annual hours, as shown on line 17 of table 9.

Section 106.40(d) requires written specifications for ingredients, containers, and closures, and is considered a collection of information. FDA estimates that the infant formula industry already establishes written specifications for these components. However, the requirements of

§§ 106.40(g) and 106.100(f)(6) may represent new recordkeeping for five (at most) plants (Ref. 12). It is not possible to predict how often a specification will not be met or how often documented reviews of reconditioned ingredients, closures, or containers will occur. FDA estimates that, on average, one senior validation engineer per plant will work about 10 minutes a week to fulfill the recordkeeping requirements of §§ 106.40(g) and 106.100(f)(6). Therefore, 5 recordkeepers x 52 weeks = 260 records and 260 records x .17 hour = 45 total annual hours, as presented in line 18 of table 9.

Records pertaining to § 106.50, the master manufacturing order and any changes to it, will be kept at the plant level. It is not possible to predict how often changes to the master manufacturing order will be made or how often deviations from the master manufacturing order will occur. Based on expert opinion, FDA estimates that each year, 5 (at most) plants will change a master manufacturing order and that, on average, one senior validation engineer for each of the 5 (at most) plants will spend about 14 minutes per week on recordkeeping pertaining to the master manufacturing order, as required by §§ 106.50(a)(1) and 106.100(e). Thus, 5 recordkeepers x 52 weeks = 260 records; 260 records x .23 hour = 60 hours as the total annual industry burden, as presented in line 19 of table 9.

The interim final rule (§ 106.55(d) and § 106.100(e)(5)(ii) and (f)(7)) requires infant formula manufacturers to make and retain records of the testing of infant formula for microorganisms. Based on expert opinion, the Agency estimates that these recordkeeping requirements represent a new collection of information for, at most, five plants (Ref. 12) and that one senior validation engineer per plant will spend 15 minutes per week on recordkeeping pertaining to microbiological testing. Thus, 5 record keepers x 52 weeks = 260 records; 260 records x .25 hour per record = 65 hours as the total annual industry burden, as presented in line

20 of table 9.

The interim final rule (§ 106.60) establishes requirements for the labeling of mixed-lot packages of infant formula. The Agency estimates that § 106.60 will require infant formula diverters to label infant formula packaging (such as packing cases) to facilitate product tracing and to keep specific records of the distribution of these mixed lot cases. (A diverter is considered to be a business or individual that purchases food, including occasionally infant formula, in a geographic area where a special allowance or deal is being offered and then resells that food at a lower price to wholesale or retail grocery, drug and mass merchandise chains in an area where the deal is not being offered.) There will be some cost associated with this recordkeeping and labeling, but the Agency estimates that this burden will be minimal as it is estimated that less than 1 percent of infant formula is handled by diverters. For the purposes of this analysis, it is estimated that it may take one worker using manual methods 15 minutes, at most, to relabel one case of infant formula, one time each month (.25 x 12 months = 3 annual hours), to meet the requirements of § 106.60(c)(2), as presented in line 21 of table 9.

The interim final rule establishes nutrient testing requirements (§ 106.91(a)(1), (a)(2), (a)(3), and (a)(4)). It is estimated that the systems and processes of 100 percent of the formula industry adhere to these provisions. Therefore, nutrient testing does not represent a new collection of information or a new recordkeeping burden as nutrient testing is estimated to be common business practice in the infant formula industry. Thus, no burden is estimated for the requirements of § 106.91(a) (Ref. 12).

The interim final rule also establishes on-going stability testing requirements (§ 106.91(b)(1), (b)(2), and (b)(3)). It is estimated that the systems and processes of the formula industry partially adhere to these provisions in that 80 percent of infant formula plants (17 of 21

plants) conduct stability testing as specified in these provisions (Ref. 12). For the 20 percent of plants (4 of 21 plants) that do not conduct stability testing as specified in this provision, it is estimated that these plants do conduct initial stability testing, but may not do so at the intervals specified in this provision (Ref. 12). For the purposes of this analysis, it is estimated that the stability testing requirements of § 106.91(b) represent a new burden of 2 annual hours, per plant. Therefore, 2 hours x 4 plants = 8 annual hours to fulfill the testing requirements of § 106.91(b) as shown in line 22 of table 9.

The requirements of §§ 106.91(d) and 106.100(e)(5) to keep records of tests required under § 106.91(b)(1), (b)(2), and (b)(3) represent new information collections for the four plants that are estimated not to be conducting all of the stability testing specified in § 106.91(b) (Ref. 12). For the purposes of this analysis, FDA estimates that, for the testing requirements in § 106.91(b), one senior validation engineer per plant will spend about nine minutes per week maintaining records to be in compliance with § 106.91(d) and § 106.100(e)(5). Thus, 4 recordkeepers x 52 weeks = 208 records; 260 records x .15 hour per record = 31.2 hours, per testing requirement, as the annual total industry burden, as presented in lines 23, 24, and 25 of table 9.

FDA estimates that all infant formula manufacturers currently conduct audits in accordance with § 106.94, but that 25 percent of infant formula plants (5 of 21 plants) do not conduct audits that include all four elements required by this interim final rule (Ref. 12). It is estimated that the ongoing review and updating of audit plans will require a senior validation engineer 8 hours per year, per plant. Therefore, 8 hours x 5 plants = 40 annual hours to regularly review and update audit plans as shown in line 26 of table 9.

The interim final rule does not mandate a frequency of auditing. For the purposes of this analysis, FDA estimates that a manufacturer will choose to audit once per week. Each weekly audit is estimated to require a senior validation engineer 4 hours, or 52 weeks x 4 hours = 208 hours per plant. Therefore, the total annual burden for the estimated five plants not currently adhering to this provision to update audit plans is 208 hours x 5 plants = 1,040 hours, as shown in line 27 of table 9.

The interim final rule requires (§ 106.96) that a manufacturer of a new infant formula establish that the new infant formula supports normal physical growth. This will require that the manufacturer either conduct a growth monitoring study (§ 106.96(b)) or demonstrate to FDA's satisfaction that the formula is entitled to an exemption from the growth monitoring study requirement (§ 106.96(c)). FDA estimates that, as a result of the interim final rule, the industry as a whole will perform one additional growth study per year (Ref. 13). The interim final rule requires that several pieces of data be collected and maintained for each infant in the growth study. It is estimated that the data collection associated with the growth study performed to comply with § 106.96(b) will be assembled into a written report and kept as a record in compliance with § 106.96(d) and § 106.100(p)(1). Thus, it is estimated that one additional growth study report will be generated as a result of this rule, and that this report will require one senior scientist to work 16 hours to compile the data into a study report. Therefore, one growth study report x 16 hours = 16 annual hours for compliance with § 106.96(d) and § 106.100(p)(1), as presented in line 28 of table 9.

The data required to be collected in a growth monitoring study will be collected for each infant at each of six visits of the study. The burden estimates for these collections have been calculated in a manner identical to that used to calculate the burden estimates for the one time

burden for growth studies of eligible infant formulas.

A study conducted according to the requirements of § 106.96(b)(2) must include the collection of anthropometric measurements of physical growth and information on formula intake and § 106.96(b)(3) requires that the anthropometric measurements be made at six times during the growth study. It is estimated that in a growth study of 112 infants, two nurses or other health professionals with similar experience will need 15 minutes per infant at each of the required six times to collect and record the required anthropometric measurements. Therefore, 2 nurses x .25 hours = .5 hour per infant, per visit, and .5 hour x 6 visits = 3 hours per infant. For 112 infants in a study, 3 hours x 112 infants = 336 hours to collect anthropometric measurement information, as presented in line 29 of table 9. In addition, it is estimated that one nurse will need 15 minutes per infant to collect and record the formula intake information. That is, .25 hour x 6 visits = 1.5 hour per infant, and 1.5 hour per infant x 112 infants = 168 hours to collect information on formula intake, as presented in line 30 of table 9.

Section 106.96(b)(4) requires plotting each infant's anthropometric measurements on the 2009 CDC growth charts. It is estimated that it will take five minutes per infant to record the anthropometric data on the growth chart at each study visit. Therefore, 112 infants x 6 data plots = 672 total data plots, and 672 data plots x .08 hour per comparison = 53.75 total hours, as presented in line 31 of table 9.

Section 106.96(b)(5) requires that data on formula intake by the test group be compared to the intake of a concurrent control group. FDA estimates that, to fulfill the requirements of this section, one nurse or other health care professional with similar experience will need 5 minutes per infant for each of the six times anthropometric data are collected. Therefore, 6 comparisons of data x 112 infants = 672 data comparisons and 672 data comparisons x .08 hour per

comparison = 53.75 total hours, as presented in line 32 of table 9.

Under § 106.96(c)(1), an infant formula manufacturer may be exempt from the requirements of § 106.96(b) if the manufacturer requests an exemption and provides assurances, as required under § 106.121, that the changes to the infant formula are limited to changing the type of packaging. A manufacturer may also be exempt under § 106.96(c)(2), if the manufacturer requests an exemption and provides assurances, as required under § 106.121 that demonstrates, to FDA's satisfaction, that an alternative method or study design is available to show that the formula supports normal physical growth in infants, that the change to an existing formula does not affect the bioavailability of the formula (including the bioavailability of its nutrients), or that the formulation is marketed in more than one form and the quality factor requirements are met by the form of the formula that is processed using the method that has the greatest potential for adversely affecting the nutrient content and bioavailability. The Agency estimates that 34 exemptions will be submitted annually and that each exemption will take 20 hours to assemble (Ref. 13). Therefore, 34 exemptions x 20 hours = 680 hours is the total annual industry burden for § 106.96(c), as presented in line 1 of table 10.

The requirements of § 106.96(f) state that a manufacturer shall meet the quality factor of sufficient biological quality of the protein by establishing the biological quality of the protein in the infant formula when fed as the sole source of nutrition using an appropriate modification of the Protein Efficiency Ratio (PER) rat bioassay. Under § 106.96(g)(1), a manufacturer of infant formula may be exempt from this requirement if the manufacturer requests an exemption and provides assurances, as required under § 106.121, that changes made by the manufacturer to an existing infant formula are limited to changing the type of packaging. A manufacturer may also be exempt from this requirement under § 106.100(g)(2), if the manufacturer requests an

exemption and provides assurances, as required under § 106.121, that demonstrates, to FDA's satisfaction, that the change to an existing formula does not affect the bioavailability of the protein. It is estimated that these requirements represent two information collections: submission of the PER results or submission of a request for an exemption when appropriate. FDA estimates that annually the infant formula industry will submit a total of 35 PER submissions: 34 exemption requests and the results of one PER study (Ref. 13).

A PER study conducted according to AOAC Official Method 960.48 will be 28 days in duration. It is estimated that there will be 10 rats in the control and test groups (20 rats total) and that food consumption and body weight will be measured at day zero and at 7-day intervals during the 28-day study period (a total of five records per rat). It is further estimated that measuring and recording food consumption and body weight will take five minutes per rat (Ref. 13). Therefore, 20 rats x 5 records = 100 records; 100 records x 0.08 hour per record = 8 hours to fulfill the requirements of § 106.96(f). Furthermore, it is estimated that a report based on the PER study will be generated and that this study report will take a senior scientist one hour to generate. Therefore a total of 9 hours will be required to fulfill the requirements for § 106.96(f): 8 hours for the PER study and data collection, and 1 hour for the development of a report based on the PER study, as presented in lines 33 and 34 of table 9. Therefore, the total recurring recordkeeping burden is 11,225.35 hours.

For the submission of the PER exemption, it is estimated that infant formula industry will submit 34 exemptions per year and that each exemption will take supporting staff 12 hours to prepare (Ref. 13). Therefore, 34 exemptions x 12 hours per exemption = 408 hours to fulfill the requirements of § 106.96(g), as presented in line 2 of table 10.

Sections 106.100(p)(1) and § 106.100(q)(1) require that, in accordance with § 106.96(d)

and § 106.96(h), the manufacturer of an infant formula that is not an eligible infant formula make and retain records that demonstrate that each infant formula meets the quality factors of normal physical growth and sufficient biological quality of protein. It is estimated that these recordkeeping requirements are fulfilled by the burden of the growth study report and PER exemption and, when necessary, the report resulting from a PER study. Thus, § 106.100(p)(1) and § 106.100(q)(1) do not represent an additional quantifiable hourly burden to manufacturers (Ref. 13).

The interim final rule implements the statutory requirement of section 412(c)(1)(A) of the FD&C Act that infant formula manufacturers register with FDA before introducing a new infant formula into interstate commerce. FDA estimates that, for each of the four firms in the infant formula industry, one senior scientist or regulatory affairs professional will need 30 minutes to gather and record the required information for an infant formula registration made under § 106.110. The annual number of registrations for a new infant formula and the number of firms that will make such registrations is not known. However, it is estimated that, annually, the industry could register 35 new infant formulas (Ref. 13), or an average of about nine registrations per firm. Therefore, to comply with § 106.110, the total annual industry burden is 35 registrations x 30 minutes per registration = 17.5 hours, as presented in line 3 of table 10.

The interim final rule implements the statutory requirement of section 412(c)(1)(B) of the FD&C Act that infant formula manufacturers make a submission complying with section 412(d)(1) to FDA before introducing a new infant formula into interstate commerce. FDA estimates that, for each of the four firms in the infant formula industry, one senior scientist or regulatory affairs professional will need 10 hours to gather and record information needed for infant formula submissions made under § 106.120. The annual number of submissions for a new

infant formula and the number of firms that will make such submissions is not known. However, it is estimated that, annually, the industry could make submissions for 35 new infant formulas, or an average of about nine submissions per firm (Ref. 13). Therefore, to comply with § 106.120, the total annual industry burden is 35 submissions x 10 work hours per submission = 350 hours, as presented in line 4 of table 10.

Section 106.121 states that manufacturers shall submit data and information to FDA in order to provide assurances establishing that a new infant formula meets the requirements for quality factors set forth in § 106.96. FDA estimates that this requirement could be satisfied by the submission of the written report of the growth monitoring study required by § 106.96(b), the burden of this provision is covered by the burden of developing the written report for a growth study. Accordingly, no additional quantifiable hourly burden is estimated for § 106.121.

The submissions under §§ 106.130, 106.140 and 106.150 must be made to satisfy the requirements of section 412(c) and (d) of the FD&C Act. Based on expert opinion, and because these submissions are currently made as required under the FD&C Act, it is estimated that the infant formula industry is adhering to these submission provisions. Furthermore, § 106.150 of the interim final rule is a consolidation recodification of current §§ 106.120 and 107.240(a) and (b), for which there is an existing OMB approval for the information collection. Therefore, no annual hourly burdens are estimated for these sections of this interim final rule.

Therefore, the total annual submission burden is 1,455.5 hours.

In compliance with the PRA, FDA has submitted the information collection provisions of this interim final rule to OMB for review. Prior to the effective date of this interim final rule, FDA will publish a notice in the Federal Register announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this interim final rule. An Agency

may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Table 9.--Estimated Hourly Recordkeeping Burden[1]

First Year Hourly Burden						
	21 CFR Section	No. of Record keepers	First Year Frequency of Recordkeeping	Total Records	Hours Per Record	Total Hours
1	Production and In-Process Control System 106.6(c)(5) and 106.100(e)(1) and (e)(3)	10	1	5	40	200
2	Controls to Prevent Adulteration due to Automatic (mechanical or electronic) Equipment 106.35(c) and 106.100(f)(5)	50	1	5	6,400	32,000
	106.94					
3	Requirements for Quality Factors For Eligible Infant Formulas--Written Study Report	4	1	4	16	64
	106.96(i)(1)(i) or 109.96(i)(1)(ii), 106.96(i)(4), and 106.100(p)(2)					
4	Requirements for Quality Factors For Eligible Infant Formulas--Anthropometric Data	896	1	2688	0.5	1,344
	106.96(i)(1), 106.96(i)(3), and					
	106.96(i)(4)					
5	Requirements for Quality Factors For Eligible Infant Formulas--	448	1	2,688	0.25	672
	Formula Intake 106.96(i)(1),106.96(i)(3), and 106.96(i)(4)					
6	Requirements for Quality Factors For Eligible Infant Formulas--	4	1	2,688	0.08	215
	Data Plotting					
	106.96(i)(1),106.96(i)(3), and 106.96(i)(4)					
7	Requirements for Quality Factors For Eligible Infant Formulas	4	1	2,688	0.08	215
	Data Comparison					
	106.96(i)(1),106.96(i)(3), and 106.96(i)(4)					

First Year Hourly Burden						
8	Quality Factors--Records	5	1	46	20	920
	106.96(i)(1)(iii) and 106.100(p)(2)					
	Total First Year Only Hourly Recordkeeping Burden	-		-	-	35,630
	Recurring Hourly Burden					
	21 CFR Section	No. of Record keepers	Annual Frequency of Recordkeeping	Total Records	Hours per Record	Total Hours
9	Controls to Prevent Adulteration Caused By Facilities-- Testing For Radiological Contaminants[2]	21	1	21	1.5	31.5
	106.20(f)(3)					
10	Controls to Prevent Adulteration Caused By Facilities-- Recordkeeping of Testing For Radiological Contaminants[2] 106.20(f)(4) and 106.100(f)(1)	21	1	21	.08	1.75
11	Controls to Prevent Adulteration Caused By Facilities--Testing For Bacteriological Contaminants 106.20(f)(3)	5	52	260	0.08	20.8
12	Controls to Prevent Adulteration Caused By Facilities-- Recordkeeping of Testing For Bacteriological Contaminants 106.20(f)(4) and 106.100(f)(1)	5	52	260	0.08	20.8
First Year Hourly Burden						
13	Controls to Prevent Adulteration By Equipment or Utensils	5	52	260	0.21	55
	106.30(d) and 106.100(f)(2)					
14	Controls to Prevent Adulteration By Equipment or Utensils	5	52	260	0.21	55
	106.30(e)(3)(iii) and 106.100(f)(3)					
15	Controls to Prevent Adulteration By Equipment or Utensils	5	52	260	0.19	49.4
	106.30(f) and 106.100(f)(4)					

16	Controls to Prevent Adulteration Due to Automatic (Mechanical or Electronic) Equipment	5	52	5	520	2,600
	106.35(c) and 106.100(f)(5)					
17	Controls to Prevent Adulteration Due to Automatic (Mechanical or Electronic) Equipment 106.35(c) and 106.100(f)(5)	20	2	10	640	6,400
18	Controls to Prevent Adulteration Caused By Ingredients, Containers, and Closures	10	52	260	0.17	45
	106.40(g) and 106.100(f)(6)					
19	Controls to Prevent Adulteration During Manufacturing	10	52	260	0.2	60
	106.50 and 106.100(e)					
		5	52	260	0.25	65
20	Controls to Prevent Adulteration From Microorganisms					
	106.55(d), 106.100(e)(5)(ii), and 106.100(f)(7)					
21	Controls to Prevent Adulteration During Packaging and Labeling of Infant Formula 106.60(c)	1	12	12	.25	3
First Year Hourly Burden						
22	General Quality Control-Testing 106.91(b)(1), 106.91(b)(2) and 106.91(b)(3)	4	1	4	2	8
23	General Quality Control	4	52	208	0.15	31.2
	106.91(b)(1), 106.91(d), and 106.100(e)(5)(i)					
	General Quality Control	4	52	208	0.15	31.2
24	106.91(b)(2) 106.91(d), and 106.100(e)(5)(i)					
25	General Quality Control	4	52	208	0.15	31.2
	106.91(b)(3) 106.91(d), and 106.100(e)(5)(i)					
	Audit Plans and Procedures	5	1	5	8	40
26	106.94--Ongoing review and updating of Audits					
27	Audit Plans and Procedures 106.94- Regular Audits	5	52	260	4	1040

28	Requirements for Quality Factors For Infant Formulas--Written Study Report	1	1	1	16	16
	106.96(b), 106.96(d), 106.100(p)(1) , 106.100(q)(1), and 106.121					
29	Requirements for Quality Factors For Infant Formulas--Anthropometric Data	224	6	672	0.5	336
	106.96(b)(2), 106.96(d), and 106.100(p)(1)					
30	Requirements for Quality Factors For Infant Formulas--Formula Intake 106.96(b)(3) and 106.96(d), and 106.100(p)(1)	112	6	672	0.25	168
31	Requirements for Quality Factors For Infant Formulas--Data Plotting	1	6	672	0.08	53.75
	106.96(b)(4), 106.96(d), and 106.100(p)(1)					
First Year Hourly Burden						
32	Requirements for Quality Factors For Infant Formulas--	1	6	672	0.08	53.75
	Data Comparison					
	106.96(b)(5), 106.96(d), and 106.100(p)(1)					
33	Requirements for Quality Factors--PER Data Collection	1	1	1	8.3	8.3
	106.96(f)					
34	Requirements for Quality Factors--	1	1	1	1	1
	PER Written Report 106.96(f)					
	Total Recurring Recordkeeping Burden	-	-	-	-	11,225.35
	Total Recordkeeping Burden					47,225.65

[1]There are no capital costs or operating and maintenance costs associated with this collection of information.
[2]This test is required no less frequently than once every 4 years.

Table 10.--Estimated Annual Submission Burden[1]

	21 CFR Section	No. of Recordkeepers	Annual Frequency of Recordkeeping	Total Records	Hours per Record	Total Hours
1	Requirements for Quality Factors GMS Exemption 106.96(c)	4	9 (8.5)	34	20	680
2	Requirements for Quality Factors--PER Exemption 106.96(g)	1	1	34	12	408
3	New Infant Formula Registration 106.110	4	9 (8.5)	35	.5	17.5
4	New Infant Formula Submission 106.120	4	9 (8.5)	35	10	350
	Total Annual Submission Hours					1,455.5

[1]There are no capital costs or operating and maintenance costs associated with this collection of information.

V. References

The following references have been placed on display in the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. We have verified all the Web site addresses in the References section, but we are not responsible for any subsequent changes to the Web sites after this document publishes in the Federal Register.

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