International Formula Council

September 5, 2014

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5360 Fishers Lane
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CITIZEN PETITION

The International Formula Council ("Petitioner" or "IFC")* submits this Citizen Petition under 21 C.F.R. § 10.30 and section 412 of the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Infant Formula Act of 1980 (IFA) and the Anti-Drug Abuse Act of 1986, to request that the Commissioner of Food and Drugs take the action requested below regarding the end of shelf-life testing requirements in the Food and Drug Administration's (FDA) Final Rule, "Current Good Manufacturing Practices, Quality Control Procedures, Quality Factors, Notification Requirements, and Records and Reports, for Infant Formula," ("Final Rule") published June 10, 2014 (79 FR 33057-33072). The Final Rule was preceded by an Interim Final Rule published February 10, 2014 (79 FR 7933-8075) and a Proposed Rule published on July 9, 1996 (61 FR 36153-36219). The IFC has previously provided comments to the FDA on both the Proposed Rule and the Interim Final Rule.

A. Action Requested

Based on new information provided in this Petition, the IFC requests that FDA reconsider the requirement in the Final Rule (under 21 C.F.R. § 106.91(b)(2)) that manufacturers of infant formula perform end of shelf-life testing on every subsequent production aggregate. The amount of testing required by the Final Rule provides no corresponding public health benefit and will have a significant negative impact on the industry. Infant formula manufacturers have significant data on the nutritional quality of existing formulas throughout shelf-life based on their long-standing and robust stability programs. Data from these programs, when reviewed across the infant formula industry over a two year period, demonstrate that all infant formulas tested meet statutory requirements for nutrient content at the end of shelf-life. Thus, we do not believe that the additional nutrient testing required under the Final Rule is necessary.[1]

Given that the compliance date of 21 C.F.R. §106.91(b)(2) is September 8, 2014, the IFC respectfully requests that the FDA:

[1] In addition, the Petitioner also requests that the Agency make modifications to §106.91(b)(2) of the Final Rule to address a possible unintended consequence related to the interpretation of the Final Rule. The Final Rule requires infant formula manufacturers to conduct end of shelf-life testing under 21 CFR §106.91(b)(2) for every "subsequent" "production aggregate" (i.e., batch). Because the term "subsequent" could be interpreted to relate back to the regulation's immediately preceding subsection, 21 CFR §106.91(b)(1), relating only to "new infant formulas," non-exempt, existing products that are not "new" appear not to be within the scope of 21 C.F.R. §106.91(b)(2). The Petitioner does not believe this was the Agency's intention.

1. Stay implementation of 21 C.F.R. § 106.91(b)(2) of the Final Rule until the Agency responds to this Petition;

2. In place of complying with the routine stability testing requirements of 21 C.F.R. § 106.91(b)(2), require manufacturers subject to the rule to continue to comply with 21 C.F.R. § 106.30(b)(3), FDA's previous requirements for infant formula stability testing, until such time as the Agency acts on this Petition; and:

3. Amend the Final Rule to incorporate relevant portions of the version of 21 C.F.R. § 106.91(b) that appeared in the Proposed Rule and the flexibility from existing 21 C.F.R. § 106.30(b)(3).

    a. In the Proposed Rule, 21 C.F.R. § 106.30(b)(3) reads:

    Stability analysis. Using representative samples collected from finished product batches, the manufacturer shall conduct stability analysis for selected nutrients with sufficient frequency to substantiate the maintenance of nutrient content throughout the shelf life of the product.

    b. In the Final Rule, 21 C.F.R. § 106.91(b)(2) reads:

    The manufacturer shall collect, from each manufacturing site and at the final product stage, a representative sample of each subsequent production aggregate of packaged, finished formula in each physical form (powder, ready-to-feed, or concentrate) and evaluate the levels of all nutrients required under § 107.100 of this chapter and all other nutrients added by the manufacturer. The manufacturer shall repeat such testing at the end of the shelf life of the product.

    c. The IFC requests that the FDA amend 21 C.F.R. § 106.91(b)(2) to read:

    Every 3 months, the manufacturers shall collect, from each manufacturing site and at the final product stage, representative samples from production aggregates of packaged, finished formula in each physical form (powder, ready-to-feed, or concentrate) and evaluate the levels for all nutrients required under § 107.100 of this chapter. The manufacturer shall conduct stability analysis for selected nutrients with sufficient frequency to substantiate the maintenance of nutrient content throughout the shelf-life of the product, which may be accomplished by repeat testing at the end of the shelf-life of the product.

B. Statement of Grounds

The IFC supports FDA's implementation of the Final Rule and the Agency's overarching public health objective to ensure the availability of safe, high quality infant formula. The IFC appreciates FDA's willingness to meet with and consider input from relevant stakeholders and the time and effort the Agency has taken to carefully draft the Final Rule. The IFC, however, has identified a revision that was made to the text of 21 C.F.R. § 160.91(b)(2) – directed at routine stability testing of infant formula – between the Proposed Rule and the Interim Final Rule (which is the same as the Final Rule) that potentially might result in significant unintended consequences with no demonstrated public health benefit.

Specifically, as set out in the Proposed Rule, § 106.91(b)(2) would have required a routine stability program to be conducted on representative samples from the final product stage of one batch of each infant formula at each manufacturing facility. In contrast, § 106.91(b)(2) of the Final Rule requires a similar routine stability program except that it requires stability testing to be

conducted on essentially each and every batch of infant formula, i.e., by requiring end of shelf-life stability testing on each production aggregate of infant formula. The Agency's definition of "production aggregate" assumes that manufacturers produce individual "batches" of infant formula that are stored separately and later combined/comingled with other stored batches when the infant formula is packaged. FDA deemed the comingling of several batches during the packaging process to constitute a "production aggregate."[2] Comingling of individual batches during the packaging process, however, is not common in the infant formula industry. Rather, the general practice is that each batch of infant formula remains separate and distinct through the final product stage and through packaging. As such, FDA's requirement that manufacturers conduct routine stability testing on each "production aggregate" essentially translates in practice to the requirement that manufacturers must conduct end of shelf-life stability testing on nearly every individual batch of formula.

As discussed in detail below, requiring stability testing on each production aggregate is not necessary to ensure the safety and quality of infant formula (as agreed by the Agency in the Preamble to the Proposed Rule), and will result in a tremendous burden on industry without a demonstrated public health benefit.

1. Consequences of Current Requirements - A Requirement to Conduct End of Shelf-Life Testing on Every Production Aggregate (Batch) of Infant Formula Adds Costs Without Commensurate Public Health Benefits

   A. Existing Stability Programs Are Effective in Assuring the Nutritional Adequacy of Infant Formulas

FDA states that routine stability testing is to ensure that an infant formula is in compliance with the nutrient requirements when released for distribution, to confirm that an infant formula contains all the required nutrients throughout its shelf-life, and to provide "continued justification for the predicted shelf-life."[3] Infant formula manufacturers have programs in place for testing the nutritional adequacy of formula both at the beginning and end of shelf-life. The initial testing at the beginning of shelf-life ensures that every production aggregate delivers nutrient levels consistent with its design and will deliver the required nutrients over its shelf-life. Nutrient delivery is also supported by other programs and processes. For example, formulas are designed considering endogenous nutrient contribution of raw materials, processing losses, nutrient addition levels, as well as stability over shelf-life.

The nutritional profile of an infant formula, like other foods, may change over time. Both the Petitioner and FDA recognize that labile nutrients will decrease over the shelf life of an infant formula. As a result, infant formula manufacturers establish the shelf life for any given form of infant formula (powder, concentrate, ready-to-use) based on nutritional data derived from stability studies for the same or similar products to assure that the nutrients in the infant formula will be above the minimum levels specified in 21 C.F.R. § 107.100 during its labeled shelf-life.

Over the years, infant formula manufacturers have accumulated extensive data from their stability programs sufficient to characterize the nutrient stability in their products over time. These data, among others, help enlighten the determination of the formula shelf life to assure compliance with 21 C.F.R. § 107.100. This information is verified and enhanced by entering new batches into their stability programs. Not every batch needs to be, or is, put on stability once the degradation profile of an infant formula is known. Because the nutritional profiles, ingredients, packaging, manufacturing processes, and manufacturing equipment for any manufacturer are similar across products, infant formula manufacturers have a large depth of experience and data on which to base safety and quality decisions.

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[2] *See id*.
[3] *Id*. at 7999.

B. Absence of Public Health Benefit

Since the promulgation of stability testing requirements in 21 C.F.R. § 106.30 in 1982, manufacturers have consistently demonstrated compliance with nutrient requirements set out in 21 C.F.R. § 107.100.

Increasing the frequency of testing at the end of shelf life from the quarterly program in place since 1982, to testing every production aggregate, would not significantly impact health for several reasons:

1. As described above, manufacturers have processes in place that ensure that infant formula products meet all nutrient requirements through the end of shelf-life.

2. An analysis of shelf-life data across the industry for the last two years, demonstrates the absence of end of shelf-life defects for released product. In this case, defects are defined as nutrient levels below the requirements specified in 21 C.F.R. § 107.100. For all non-exempt infant formulas tested, none of the production aggregates that reached end of shelf-life in 2012 or 2013 were found to be "defective". Approximately, 10% of all production aggregates were tested at the end of shelf-life over this time period.

3. Even though end of shelf-life defects have not been observed for released product, an infant would be highly unlikely to consume product only at the end of its shelf-life. Further, based on the frequency of manufacture and store inventories, virtually all infant formula is consumed early in its shelf-life (consumers typically purchase and use infant formula between 3 and 9 months after manufacture and do not stockpile infant formula at home).

As the Agency has recognized in other contexts (most notably the fundamental concept that underpins the proposed FSMA rules and the drug and dietary supplement GMPs), product safety and quality is controlled by implementing appropriate procedures and controls during processing rather than through finished product testing – including end of shelf-life testing. Consequently, routine end of shelf-life stability testing cannot and is not intended to ensure that a currently marketed product meets its specifications (because the testing occurs after expiry and the product presumably is no longer on the market). Therefore, by its nature, routine end of shelf-life stability testing can only provide an incremental benefit – *i.e.*, justifying the existence of a shelf-life that was previously established through a rigorous comprehensive stability program.

While the infant formula stability testing program that is set out in 21 C.F.R. §§ 106.91(b)(1) and (b)(2) is similar to the drug GMP stability testing program in 21 C.F.R. § 211.166 because it requires a comprehensive stability assessment designed to determine shelf-life, followed by scientifically justified routine testing, not even the drug GMPs require routine stability testing of each batch (i.e., each production aggregate) of finished product. Instead, the drug GMPs provide for flexibility by requiring that "an adequate number of batches of each drug product…be tested."[4] Given the strict regulatory requirements for the identity, strength, quality, and purity of drug products through product expiry, it seems unlikely that FDA intended to require routine stability testing for infant formula that is more stringent than the routine stability testing required for finished pharmaceuticals, especially in light of the rigorous in-process controls and testing procedures required in the infant formula Final Rule that do, in fact, establish the safety and quality of infant formula. As stated above, the IFC believes this apparent departure stems not from a change in how the Agency views stability testing but rather from a misunderstanding of

[4] 21 C.F.R. § 211.166(b).

how manufacturers produce infant formula, namely – manufacturers do not routinely commingle batches into a production aggregate.

C. If Every Batch of Infant Formula Has to Be Tested at the End of Shelf-Life, It Will Have a Severe Financial Impact

In explaining why it was requiring testing of each production aggregate, FDA identified several factors that play into the nutrient stability of an infant formula, including the form (powder, ready-to-feed, or concentrate), the matrix of the formulation, processing techniques, packaging, and the manufacturing facility.[5] These factors for infant formula, however, remain the same across different production aggregates of the same product. Therefore, there is minimal, if any, benefit received by conducting routine stability testing on each similar production aggregate at the end of shelf-life. And, this expanded testing requirement comes at an exorbitant cost, as it would require additional testing, laboratory equipment, storage facilities, building construction, and personnel.

Based on current industry practices and production, we have estimated the potential costs of the shelf-life testing requirements of the final rule on the industry. These estimates are presented below:

The total estimated first year cost: $20,583,400

- **Estimated one-time capital costs: $4,300,000**
  - Estimated capital costs to increase instrumentation to handle additional capacity of increased samples: **$2,100,000**
    - Includes additional instrumentation such as high-performance liquid chromatography, mass spectrometers and other analytical instruments
  - Estimated capital cost to increase storage facilities to account for increased number of samples: **$2,200,000**
    - Construction of these additional facilities will require 3-6 months with up to 16,500 additional square feet of space necessary per manufacturing plant
- **Estimated annual costs: $16,283,400**
  - Estimated total annual cost for additional testing based on standard contract lab costing:
    - Includes the estimated annual incremental cost of:
      1. Conducting increased testing;
      2. Increased personnel; and
      3. Laboratory fees.
  - Estimated incremental number of full-time employees needed to handle capacity of the increased sample number: **36** (for three member companies)
    - Includes personnel with expertise in laboratory analysis

D. The Agency acknowledged in the preamble to the Proposed Rule that routine stability testing of each batch (i.e., each production aggregate) of infant formula was not necessary to ensure safety and quality.

As originally proposed, the routine stability testing requirements in 21 C.F.R. § 106.91(b)(2) would have required the testing of a representative sample from the final product stage of a batch of each form of infant formula at each manufacturing facility.[6] The original provision did not require routine stability testing of each batch (i.e., each production aggregate) of infant formula because

[5] 79 Fed. Reg. at 7998.
[6] 61 Fed. Reg. at 36214.

FDA expressly acknowledged that "quarterly testing of infant formulas for nutrient stability [was] currently conducted by the industry" and the Agency was "not aware of any problems that have resulted from this frequency of testing."[7]

In the Interim Final Rule, however, FDA revised 21 C.F.R. § 106.91(b)(2) to require routine stability testing of each batch (i.e., each production aggregate) of infant formula.[8] The IFC is not aware of any data in the public record[9] that refutes the basis of FDA's original conclusion or industry's most recent stability data. Moreover, there is ample robust evidence that supports the flexible routine stability testing program that the Agency originally proposed in 21 C.F.R. § 106.91(b)(2).[10] The easiest explanation for this omission is that the Agency did not, in fact, intend to require manufacturers to perform routine stability testing on essentially every batch of infant formula. Rather, the Agency believed that industry commingled batches into a production aggregate.

E. IFC's proposed revisions to 21 C.F.R. § 106.91(b)(2) are consistent with section 412 of the FFDCA.

Section 412(b)(2) of the FFDCA sets forth the good manufacturing practices (GMP) and quality control procedures that the Agency is required to establish by regulation to ensure that an infant formula provides nutrients in accordance with the FFDCA and is manufactured in a manner designed to prevent adulteration. Notably, section 412(b) includes several mandatory requirements that must be conducted on "each batch of infant formula," including the requirements that serve as the basis of the Final Rule's comprehensive stability testing program in 21 C.F.R. § 106.91(b)(1)(i).[11]

In contrast, section 412(b)(2)(B)(ii) of the FFDCA, which is the basis for the Final Rule's routine stability testing in 21 C.F.R. § 106.91(b)(2),[12] requires only that there be "regularly scheduled testing…of samples of infant formulas during the shelf life of such formulas to ensure that such formulas are in compliance with this section." As such, Congress provided FDA with certain flexibility to implement that provision as appropriate. As discussed above, this type of flexibility is reflected in the proposed rules promulgated under the Food Safety Modernization Act and the GMP stability testing requirements for drugs and dietary supplements. The IFC's proposed revisions to 21 C.F.R. § 106.91(b)(2), therefore, are consistent with the statute, as well as the approach FDA has taken with respect to routine stability testing for other types of products.

2. Summary

The IFC believes that the additional requirements for end of shelf-life testing under the Final Rule are unnecessary and burdensome and do not provide any additional public health benefit for the reasons provided in this Petition. We therefore request that the Agency amend 21 C.F.R. § 106.91(b)(2) to read:

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[7] *Id*. at 36176.
[8] *See id*. at 8066.
[9] As FDA is aware, Executive Order 13563 requires that regulations must: (1) be evidence-based and "based on the best available science"; (2) "promote predictability and reduce uncertainty"; (3) be "the least burdensome"; (4) be based on "approaches that maximize net benefits"; and (5) have benefits that justify the costs. *See* 76 Fed. Reg. 3821 (Jan. 21, 2001).
[10] The most recent industry data, discussed above in section B.1.A.2, confirm that there were no observed deviations in the end of shelf-life testing of infant formula in 2012 and 2013. These recent data support the Agency's original flexible stability testing program and confirm FDA's original conclusion in the preamble to the Proposed Rule that the Agency had not identified any deficiencies with the routine stability testing programs already being followed by industry.
[11] *See, e.g.*, 21 C.F.R. §§ 106.91(b)(2)(B)(i), (b)(2)(B)(iii), and (b)(3).
[12] FDA explains in the preamble to the Interim Final Rule that "the provisions of proposed § 106.91(b) implement section 412(b)(2)(B)(ii) of the FD&C Act." 79 Fed. Reg. at 7996.

(b)(2) Every 3 months, the manufacturers shall collect, from each manufacturing site and at the final product stage, representative samples from production aggregates of packaged, finished formula in each physical form (powder, ready-to-feed, or concentrate) and evaluate the levels for all nutrients required under § 107.100 of this chapter. The manufacturer shall conduct stability analysis for selected nutrients with sufficient frequency to substantiate the maintenance of nutrient content throughout the shelf-life of the product, which may be accomplished by repeat testing at the end of the shelf-life of the product.

C. Environmental Impact

The actions requested herein are subject to categorical exclusion under 21 C.F.R. § 25.30 and § 25.32.

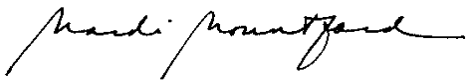
D. Economic Impact

Pursuant to 21 C.F.R. § 10.30(b), an economic impact statement concerning the effect of the requested actions will be submitted only at the request of the Commissioner. However, as noted above, if the Petition is not approved and 21 C.F.R. § 106.91(b)(2) remains as it is stated in the Final Rule, the financial impact on industry will be immense.

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the Petitioner and which are unfavorable to the Petition.

Respectfully submitted,



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