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INTERNATIONAL

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville
MD 20852
UNITED STATES OF AMERICA

Dear Sir:

Current Good Manufacturing Practice, Quality Control Procedures, Quality Factors, Notification Requirements, and Records and Reports for the Production of Infant Formula; Reopening of the comment period – Docket No 95N-0309.

1. The Food and Drug Administration's announcement in the Federal Register, Volume 68, Number 81, dated April 28 2003, invited further comments on proposed new rules governing the production of infant formula. The comment period has been reopened to update comments and receive new information.

2. SHS International Ltd submitted written comments on the proposed rule published in the Federal Register July 9 1996. Please refer to our letter dated 5 December 1996. As requested, we have not repeated all of these comments but have responded specifically to the issues raised in the request for comments of 28 April 2003.

I. General Comments – cGMP and Quality Control Procedures

3. SHS International Ltd is a manufacturer of several exempt infant formulas not available at retail level (i.e., formulas not generally found on retail shelves for general consumer purchase, that must be requested from a pharmacist or be provided by institutions such as hospitals or clinics). These formulas are distributed in the U.S. by our wholly owned subsidiary, SHS North America. The comments we have made consider the impact of the proposed regulations on the manufacture of exempt infant formula.

4. While SHS welcomes moves by the Agency to further clarify the regulations governing infant formula, we would like to request that the Agency acknowledge in these regulations that

exempt formulas[1/] are statutorily exempt from regulations establishing quality factors, good manufacturing practice and quality control procedures.[2/] Without this regulatory clarification, FDA inspectors too often utilize requirements for conventional infant formulas as a checklist for inspections of facilities manufacturing exempt infant formula. It is important to recognize that this exemption was enacted by Congress in order to encourage manufacturers to commit resources to the development, manufacture, and availability of innovative formulas for infants with special needs that cannot be met by conventional formulas.[3/] Given the much smaller patient populations, manufacturers of these products tend to be smaller companies that require greater regulatory flexibility, in order to provide these much needed products. SHS believes that exempt infant formulas not available at the retail level (hereafter referred to as "special infant formulas") should be manufactured to a high standard of quality, but that it is important to recognise and acknowledge that manufacturers can ensure the quality of these products through alternative quality control procedures.

5. SHS would like to request that the Agency include in its preambular discussion that manufacturers of special infant formulas should be encouraged to comply voluntarily with the cGMP/quality control/quality factor requirements of Part 106 (subparts B, C, and E), but that statutory exemption from these requirements is afforded to these products under the Federal Food, Drug, and Cosmetic Act ("FFDCA" or "the Act") and 21 C.F.R. § 107.50(c). In inspections of manufacturers of special infant formulas, the Agency should accept alternative quality control activities, provided those activities are documented and demonstrate that the product meets the nutrient requirements of the Act (or infant formula notifications filed with, and accepted by, the Agency) and are otherwise manufactured in a manner designed to prevent adulteration.

II. Specific Comments to Issues Raised – cGMP and Quality Control Procedures

Although the proposed quality factor/quality control regulations are not specifically applicable to SHS's special infant formulas, given Agency policy of using Part 106 as a point of reference for exempt infant formula manufacture activities, the Company has the following additional comments on the specific issues raised in the April 28, 2003 Federal Register. The Company further reiterates its view (expressed in its December 1996 comments) that these provisions of Part 106 would be inappropriate to apply to special infant formulas, even as guidance.

1/ These are defined as those represented and labelled for use by an infant "who has an inborn error of metabolism or a low birth weight," or "who otherwise has an unusual medical or dietary problem."

2/ Section 412(h) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 350a(h).

3/ H.R. Rep. No. 95-963, at 10 (1980).

Issue 1. – E. sakazakii

6. SHS does not believe that required microbiological testing specifically for *E. sakazakii* is necessary to ensure the safety of powdered infant formula and to prevent future outbreaks. *E. sakazakii* is a member of the *Enterobacteriaecae* family, which includes other pathogenic and opportunistic pathogenic organisms. The safety of infant formula would be better assured by employing stricter criteria for the testing of the family *Enterobacteriaecae* as a whole. We suggest that the analytical procedure be changed from a quantitative analysis to a presence/absence test for *Enterobacteriacae* (which includes *E. sakazakii*). An appropriate level of assurance would be achieved by setting a criterion of 0 in a 10 g sample.

7. There are other changes to the proposed microbiological requirements that should be considered to ensure the safety of powdered infant formula. It is the view of SHS that reducing the risk of environmental microbiological contamination is a better strategy than increased end-product testing. HACCP procedures should be routinely used to identify the risks of microbiological contamination in the manufacturing process. Regular environmental monitoring for *Enterobacteriaecae* will reduce the risk of contamination of powdered formulas, while at the same time helping to rapidly identify the source of any contamination. Routine environmental monitoring for presence of *E. sakazakii* specifically should not be necessary.

8. SHS manufactures special infant formulas used from birth and which may also be introduced to older infants. However, we recognise that our formulas may be used in infants who are "at risk," not only because of their age, but because of their medical condition. We would therefore apply the same strict criteria for *Enterobacteriacae* to all of our special infant formulas.

Issue 2 – Use of probiotic organisms

9. If probiotic organisms such as *Streptococcus thermophilus* are added to infant formula, they are likely to be required at a level in the product of 10^9 to 10^{12} per gram of powder. Additional probiotic organisms would need to be added to maintain the effective level over the shelf-life of the product. The aerobic plate count (APC) thus would exceed that currently proposed in 21 C.F.R. § 106.55 (10,000 CFU/g).

10. To ensure that a high APC is caused by the added probiotic organism and not by contamination of the formula, there would need to be a two-stage testing procedure. Prior to addition of the probiotic organism, the bulk product would have to be sampled and the aerobic plate count measured. Selective microbiological test regimes then would have to be carried out on final packaged product.

Issue 3 – Changes in current activities required by proposed regulations

11. Separation of operations -- In the current proposal, Section 106.20(b) requires that separate areas be designated for holding raw materials, in-processing materials, and final product infant formula, dependent upon their test status (that is, on test and pending disposition, released for use or failed for use or distribution). The aim of this provision is to reduce the potential for use of failed materials and the release for sale of failed (or on test) finished product. In our view, physical separation is not necessary to prevent potential use of failed materials and is particularly over-burdensome for smaller manufacturing facilities, where the cost of additional warehousing space would be prohibitive. Additionally, the constant movement of materials could cause problems with quality in itself such as spillages.

We suggest that physical separation should not be required, but that each manufacturer must establish effective and documented procedures for the proper designation, holding and release of materials during all stages of production. SHS has implemented a computerised control system to ensure safe use of materials, which has proved to be an effective means of controlling the safe handling of our products.

We estimate that the cost of building additional warehousing space to accommodate the requirements of material separation would be approximately $2 million.

12. Air filtration systems -- SHS has air filtration systems located in all areas of the manufacturing plant where infant formula or raw materials may be exposed to the atmosphere. These filter all incoming air using pleated filters and/or bag filters to remove particulate matter. In addition to the air handling systems employed, we have an extensive monitoring program, which ensures that the systems in place are maintaining an acceptable level of air quality in our manufacturing areas. The Agency should consider the prohibitive cost and level of disruption which would be encountered in changing air filtration systems to meet an increased specification, which are currently performing to an appropriate standard and pose no risk to infant formula products.

Issue 4 – Validation of automatic systems

13. SHS agrees that there should be a requirement that equipment is designed, installed, tested and maintained in a manner that will ensure that it is capable of performing its intended function of producing and analyzing infant formula. However, the term "validation" is generally used in the pharmaceutical industry in relation to the degree of accuracy that is required in manufacturing specific chemical entities which are potentially toxic. The level of accuracy required or indeed possible to achieve in the manufacture of foods and, specifically, infant formula does not warrant the degree of evaluation of process suggested by the term "validation."

14. The requirements for in-process, final product and stability testing currently required for infant formula are exacting and allow very little variance within the manufacturing process. In this respect, the methods used are tried and tested and the results obtained reflect this. If the Agency intends to require validation of all mechanical and electronic processes used in the manufacture of infant formula, we would suggest that this not be required retrospectively for processes that have been used successfully for many years. It should apply to significant changes to equipment or processes that are critical to the manufacture of the infant formula going forward. The manufacturer is best placed to determine what testing is appropriate to that piece of equipment related to the specific change and whether it is critical to the manufacture of the infant formula.

III. General comments – Quality Factors

15. SHS welcomes the Agency's move to clarify the quality factor requirements of the Act. It is essential that the health of vulnerable infants is protected. However, it is also important that, to the extent FDA uses these regulations governing clinical testing as a guide for special infant formulas, the regulations do not become so burdensome that innovative new formulas for infants with specific nutritional requirements as a result of their medical condition, are not made available to infants in the U.S.

16. There are a number of reasons, which we have outlined below, why the quality factors acceptable for special infant formulas are different from those required to support the use of a formula in healthy infants. We would therefore like to propose that the regulations incorporate (either in proposed Part 106 or by reference to Part 107.50 on exempt infant formulas) a statement to the effect that special infant formulas are not subject to the specific quality factor requirements set forth in 21 C.F.R. §§ 106.96 and 106.97, provided that manufacturers of these products have an appropriate, alternative quality control program.

IV. Specific comments to issues raised – Quality Factors

Issue 6 – Quality factor measures for infant formula

17. The Agency requested comments on the appropriateness of the quality factors proposed (protein quality and normal growth) and any comments on other quality factors that could be implemented to be consistent with current scientific knowledge. Comments were requested in light of several meetings that have taken place of the Food Advisory Committee ("FAC") and its subcommittees. Again, while regulations promulgated pursuant to Section 412(b) of the FFDCA are not specifically applicable to exempt infant formulas not available at the retail level, SHS has the following comments on the requirement for these quality factors in relation to these special infant formulas.

18. One of the quality factors proposed by the Agency is evidence that the formula supports healthy growth when fed as a sole source of nutrition. It may be considered that this can be demonstrated by feeding a special infant formula designed for a specific medical condition to newborn healthy infants in line with current CON/AAP Task Force recommendations. Indeed, this would save time and would overcome some of the inherent difficulties in recruiting and studying sick infants. However, SHS strongly believes that special formulas should be tested in the target population group and not in a group of healthy infants. Biomedical research must be preceded by careful assessment of foreseeable benefits to the subject or to others, as required under the Declaration of Helsinki. While sick infants for whom the formula is intended should benefit from the introduction of a new or improved infant formula designed for their specific medical condition, healthy infants almost certainly will not. For some special infant formulas it is not possible, for nutritional reasons, to feed them to healthy infants, for example, formulas designed for the management of metabolic diseases. For other formulas, there is no requirement and no benefit to the healthy infant of conducting such a clinical study. The results cannot necessarily be extrapolated to the population of sick infants for which the product is intended. It is also not possible to measure other disease-related outcomes which may be equally as important in a specific disease as growth. SHS considers that testing special infant formulas in healthy infants is neither ethical nor practical.

19. It is also important to recognise that, where clinical trials are conducted in the patient group for which the product is intended, it may not be possible to meet all the requirements of the protocol and study design currently proposed in Section 106.97. Hence, SHS requests that these regulations acknowledge the need for flexibility in the study of special infant formulas.

20. In most instances, it will not be possible or desirable to feed a special formula as a sole source of nutrition from 14 days or 1 month of age, over a 4 month period for the following reasons:

i) The management of metabolic disease will almost always require the supplementation of formula with either breast milk or standard infant formula.

ii) The age of diagnosis of different medical conditions will vary. Thus, the age of inclusion in a study will reflect this and where infants are older, they will necessarily be taking at least some complementary foods in the diet. SHS feels that it is not ethical to interfere with best clinical practice and that the trial design needs to reflect actual practice.

21. Growth will be a major outcome of any study in infants. However, for special infant formulas it is important to recognise that growth is not just related to the nutritional adequacy of the formula, but also to its ability to alleviate the symptoms of disease which may adversely affect growth. The inability to test growth when the formula is used as a sole source of nutrition can be

compensated for by including additional outcome measures such as biochemical/haematological, developmental scores and clinical disease outcomes.

22. SHS recognises that weight is the most sensitive indicator of growth in a healthy newborn infant. However, in infants with a specific medical condition, particularly where they are recruited in the second half of infancy, linear growth may be a more sensitive indicator than weight. Rate of weight gain decreases in older infants who are more active and changes in individual weights become more difficult to interpret. It is important to recognise that growth also may be affected by the medical condition concerned.

23. The Agency states in the preamble to Section 106.97 that, although randomised, double blind controlled trials are the most desirable in testing the ability of an infant formula to maintain normal growth, it may not be possible to conduct these in certain cases for exempt infant formula. SHS welcomes this recognition and supports the fact that, wherever possible, a randomised controlled trial should be conducted. However, the selection of a suitable control group and control formula is not always possible or ethical, and, in some instances, infants may have to act as their own controls. Healthy breast-fed or formula-fed infants are generally not appropriate controls, particularly where a clinical outcome is being measured and compared. Flexibility in trial design, dependent on the disease and population group, is essential.

24. The two FAC meetings that have discussed the issue of growth studies have involved some discussion on the power of studies to detect a difference in growth between study groups and the number of patients required to be recruited. Power calculations rely on the use of systematic reviews of available data and pilot studies, in deciding on the size of differences in measures regarded as clinically important and the anticipated variability of these measures. Such information may not be available for sick infants, and extrapolating from data on healthy infants can be misleading. Lack of information on which to base a power calculation for a clinical study involving sick infants means that it may not be possible to determine the required sample size by means of a power calculation in advance of a clinical study. There also may be cases where a power calculation is possible, but the low incidence of the disease limits the number of patients who can be recruited in a reasonable timeframe to a particular study.

25. The FAC meetings have discussed the extrapolation of data collected in one group to other population groups and whether this is acceptable practice. As stated in paragraph 19 above, SHS does not consider it acceptable to extrapolate from healthy infants to sick infants. However it should be possible for manufacturers to extrapolate data from a clinical study of an infant formula in the population for which it is intended to other comparable groups of sick infants. Assessment of the merits of such extrapolations should be made on a case by case basis. For example, it should be possible to extrapolate data from a clinical study on a new formula for

Phenylketonuria, where it is possible to recruit a reasonable number of patients in a reasonable time frame, to other metabolic conditions with a similar dietary management in which the low disease incidence does not permit generation of meaningful group data e.g., MSUD.

Issue 6 (a) – Clinical trial requirements for new or reformulated infant formula

26. SHS supports the view that a completely new infant formula should be required to demonstrate growth and other clinical benefits in an infant population. For a reformulated infant formula, however, there are many different types of changes that may be made for a variety of different reasons (e.g., regulatory, nutritional – based on new evidence or guidelines, supply of ingredients). It is not practical or ethical to repeat trials in infants, particularly in infants who are unwell, unless on review of the changes, the manufacturer would predict, based on theory and experience, that the change may affect growth and development. From the point of view of special infant formulas, for the reasons outlined above, it is not normally possible to perform trials in very young infants with the formula as sole source of nutrition. Therefore, the likelihood of detecting a difference in growth between two formulas as a result of changes in formulation is small. For special infant formulas specifically, we would suggest that other means of demonstrating equivalence should be acceptable. For example, this may be an instance where balance studies could be more usefully employed to assess the impact of macronutrient changes.

Issue 6 (b) – Use of National Centre for Health Statistics growth charts

27. Specialised infant formulas are often designed for small numbers of patients and in order to make them viable, they are marketed globally. The current draft of the proposed rule assumes that clinical studies of infant formula are conducted solely in the U.S. SHS does not always perform clinical trials in the U.S. but may work with specialist centres in Europe and other countries. It should not be a pre-requisite that a study is carried out at a U.S. centre, particularly for special infant formulas. If this is the case, then the reference population against which growth data from clinical trials is assessed should be appropriate to the age and birth country of the infants studied. For example, it would be appropriate to compare the growth of infants in a multi-centre European study with a European reference population (e.g., the Euro-Growth standards, 2000)[4/] rather than an American reference population.

Issue 6 (c) – Age of enrollment

28. We have addressed the issue of age of enrollment of infants requiring special formulas in paragraph 20 (ii). It is unlikely that patients with certain medical conditions could be enrolled within the first month of life.

4/ Haschke F, van't Hof MA, Euro-Growth Study Group. Euro-Growth references for length, weight, and body circumferences. *J Pediatr Gastroenterol Nutr.* 2000; 31: S14-S38.

Issue 7 – The clinical study protocol

29. The Agency has stated its intention to remove the provisions for clinical trial protocols from Section 106.97(a)(1)(ii). SHS supports the Agency's view that this information is better presented as a guidance document, on setting forth recommendations for clinical study protocols for infant formula submitted as part of an infant formula notification under Section 412(c) of the Act. We request that the Agency make reference in any such guidance document to the fact that exempt infant formulas may deviate from the recommendations, where there is a good scientific, technical, medical or nutritional rationale for doing so.

30. The Agency proposes that any final rule that may be issued based on the proposal become effective 120 days after its date of publication. The clinical trial of infant formulas takes a number of years from initiation. There will currently be trials underway that may not comply fully with recommendations made in the future on study design and protocol. We request that such trials commenced before the date of publication of the final rule and any associated guidelines be allowed some flexibility in their content as long as the overall aim of collecting reliable data is achieved.

V. Conclusion

SHS has several specific requests in relation to the text of the proposed Part 106 which will ensure that manufacturers are able to continue to provide quality exempt infant formulas in the U.S. without unnecessarily onerous regulation.

i) Include in proposed Section 106.1 (Status and Applicability of the regulations in part 106) a statement to the effect that manufacturers of exempt infant formula not available at retail level are exempt from the requirements of Part 106, subparts B, C, and E, under Section 412(h) of the FFDCA and 21 C.F.R. §107.50(c), and shall establish adequate means of assuring that the product meets the nutrient requirements of the Act (or notification filed with, and accepted by, the FDA) and is otherwise manufactured in a manner designed to prevent adulteration.

ii) Include in the preamble to Part 106 of these regulations the recommendation set forth at paragraph 5 of this letter.

As we stated in 1996, SHS is committed to the supply of quality exempt infant formulas, but requests that the Agency recognise the impact of the proposed regulations on exempt infant formula manufacturers. Exempt infant formula manufacturers do not receive market incentives as do other products intended for rare diseases or conditions (i.e., orphan drugs) and, thus, it is important not to add regulatory requirements that will further discourage manufacturers from committing resources to this vital public service.

We appreciate the Agency's consideration of our comments and hope that they prove useful to the consultation process and finalisation of the rule. Please do not hesitate to contact us if you require any further information or clarification.

Yours faithfully
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