Docket No. 95N-0309

Anderson, Shellee

From: Punia, Mandeep (DHS-WIC) [MPunia@dhs.ca.gov]
Sent: Monday, June 30, 2003 6:52 PM
To: Anderson, Shellee
Cc: Sechrist, Andrea (DHS-WIC)
Subject: Comments on the Proposed Rule

Importance: High

FDA RESPONSE to
'ROPOSED FORMU..

We would appreciate if you would accept the attached comments from the California WIC Program.

<<FDA RESPONSE to PROPOSED FORMULA REGS.doc>>

Thanks.

Sincerely,
Mandeep Punia
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RESPONSE FROM THE CALIFORNIA WOMEN, INFANTS AND CHILDREN (WIC) SUPPLEMENTAL NUTRITION PROGRAM

FEDERAL REGISTER
FOOD AND DRUG ADMINISTRATION
PROPOSED RULE; REOPENING OF THE COMMENT PERIOD
COMMENTS DUE BY JUNE 27, 2003

It appears that ingredients, such as probiotics are part of this request for comment, but only as related to processing and microbial levels.

ISSUE 1: Should FDA include a microbiological requirement for the bacteria E. sakazakii? If so, what requirement should the agency consider to ensure the safety of powdered infant formula and prevent future outbreaks?

RESPONSE: Manufacturer testing for microbes has generally been sufficient for the past infant population. However, there has been a change in the infant population who consumes powdered formula. Premature infants are now viable at micro weights and extreme prematurity of less than 23 weeks gestation. Because this population has increased exponentially in numbers, and they have special needs i.e. immature gastrointestinal function and barriers, they are more subject to microbial infection. The E. sakazakii bacteria was an issue in April 2001 in case of a neonate, and the commercial powdered formula implicated was recalled by the manufacturer.

Formula intended for premature infants or formula for infants who have medical conditions that relate to decreased gastrointestinal barriers should have additional microbial testing and higher standards in order to address the potential and known risks of this population. These formulas should receive specific and elevated testing and be labeled as such to inform families and practitioners of their sterility.

ISSUE 2: What changes, if any, in the proposed microbiological requirements would be appropriate to provide for powdered infant formula and to ensure its safety if microorganisms are intentionally added to infant formulas?

RESPONSE: The testing would need to be specific for the type of organism added in order to evaluate for all other unintentional microbes on an institutional basis.

More important issues/questions are:

- Is it necessary to add probiotics to infant formulas whether they are generally regarded as safe (GRAS) or not? FDA should thoroughly evaluate and

confirm that these substances are safe for preterm infants (the at-risk population) with under-developed gastrointestinal barriers.

- What is the expected outcome of adding new ingredients to infant formula?
- Is it realistic to use an outcome or goal of trying to approximate the composition of breastmilk?

ISSUE 3: What new activities would manufacturers have to undertake to comply with the proposed regulations? What activities would manufacturers have to discontinue to comply with the proposed regulations?

RESPONSE: No comment other than it appears more processing refinement and further separation of processing will be needed.

ISSUE 4: What proposed validation requirements are needed for automatic systems after the modification and before use of the modified system to manufacture commercial products?

RESPONSE: Sufficient sampling on a pre- and post-implementation basis would be needed in order to determine if the new system is meeting the targeted microbial detection levels (based on data of known levels of microbes). Periodic batch testing should continue on a prescribed basis in order to detect malfunctioning.

ISSUE 5: How often and under what conditions should manufactures now calibrate instruments and controls against a known standard and what is the adequacy of current procedures?

RESPONSE: Given that more specificity is required and that this is "sole source of feeding" for a high risk population, the calibration needs to be high and frequent. Frequency is increased due to the nature of the issue, considering that microbes are ubiquitous in the environment and the medium in question (formula) is ideal for bacterial growth.

ISSUE 6: What is the appropriateness of quality factors: protein quality and normal physical growth that could be implemented to be consistent with current scientific knowledge?

- **What requirements should the agency establish to determine when manufacturers must conduct clinical growth studies for a new or reformulated infant formula?**
- **Should FDA require that manufacturers compare their clinical study growth data with the National Center for Health Statistics (NCHS) growth charts and the Iowa reference data?**

RESPONSE: Benchmarking is critical for evaluating and measuring the appropriateness of experimental factors. Protein quality and physical growth are

very basic benchmarks and do not match the present ingredient changes initiated by formula manufacturers. These limited criteria do not evaluate the effect of adding long chain polyunsaturated fatty acids and probiotics to infant formula.

Because of the increasing complexity of formula ingredients, it is more relevant to evaluate overall nutrient quality and availability, minimally for targeted vitamins, minerals, as well as the three macronutrients.

Additionally, using national data that reflects the diversity of population should be used. Iowa has historically not represented diverse populations. We recommend adding a longitudinal benchmark and request clinical studies occur with larger/diverse population groups over a longer period of time.

ISSUE 7: In the clinical study protocol, remove the review and approval by an Institutional Review Board (IRB) and the written informed consent from parents or legal representatives of the infants. Instead a guidance document on what is recommended for the clinical study protocol for infant formula is proposed.

RESPONSE: Considering that the infant population is becoming more complex and more diverse, additional checks and balances are imperative by an independent body such as the IRB. As formula choices and their respective ingredients become more complex and less understandable by the public, an attempt to obtain informed consent from parents who are providing an experimental formula as a sole source feeding is essential. Lastly, manufacturers should comment on those infants that fall out of the study when reporting the results of clinical trials.