Is It Time to Put a Moratorium on New Infant Formulas that Are Not Adequately Investigated?

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Infant formula development in the US is an ongoing process of development and regulation. For many years, there were few infant formulas in use in the US. Formulas were either "routine" cow milk protein-based, soy protein-based, or uncommonly, specialized formulas such as those for infants with a documented cow milk protein allergy or metabolic diseases. Decisions about formula selection were almost entirely at the discretion of a child's pediatrician, and public advertising and marketing of infant formulas was not done or was extremely limited. This changed in the late 1980s with the introduction of several new formulas and a new infant formula company to the US marketplace. Currently, virtually every infant formula company in the US markets directly to consumers using a large range of media.[1]

Formulas with or without slightly different components are being released on a regular basis. Sometimes "older" marketed names are used; in other cases new names are introduced. There is no database for the public or pediatricians to track these introductions. However, many such changes and additions are occurring every year. Advertising is intense, and, in the US, includes the use of websites targeted directly to the consumer. The consequences of this marketing on both consumer and pediatric caregiver behavior have not been extensively studied, although limited data suggest it may affect consumer's willingness to change formulas.[2] Nonetheless, it is not surprising that there is considerable consumer confusion about choosing infant formulas, and it is almost impossible for any family member or even their pediatrician to know the subtle differences among formulas on the store shelf.

In this discussion, I will consider specific issues related to new and modified infant formulas, some consequences of the changes in formula composition and marketing in recent years, and question whether the population might best be suited by slowing down the introduction of new formulas until clearer guidance and research are available about these formulas.

AAP	American Academy of Pediatrics
FDA	Food and Drug Administration
IFA	Infant Formula Act
IOM	Institute of Medicine
USDA	US Department of Agriculture
WHO	World Health Organization
WIC	Special Supplemental Nutrition Program for Women, Infants, and Children

Regulatory and Other Guidance Related to Infant Formulas and Their Marketing in the US

Statutory and Food and Drug Administration Regulations

The modern regulatory era began with a law, called the Infant Formula Act (IFA), passed in 1980 and amended in 1986. This act set standards for the production and testing of infant formulas and was developed primarily because of a serious incident in which chloride was inadequately provided in some batches of infant formula.[3] Further Food and Drug Administration (FDA) guidance established regulations for the introduction of new infant formulas and changes to existing formulas. These regulations were most recently updated and finalized in its current form in and made effective on July 10, 2014.[4] These recent changes were mostly technical related to formula preparation and safety testing but did contain relatively minor new guidance describing testing process related to the introduction of new formulas or changes in existing formulas.

The most common misconception about the development and release of new infant formulas is that all changes in infant formulas are extensively tested by the manufacturer and then are approved by the FDA based on substantial clinical data. This is inaccurate and leads to the perception that all marketed infant formulas are not only safe but have health benefits compared with alternative formula options as described by their marketing description.

The FDA does not "approve" infant formulas. This surprises almost everyone but is an accurate description of the FDA process. Rather, they review the proposed formula composition and explanation of use that has been provided by the formula company and then relay any concerns about the marketing of the product to the company. This distinction is more than just semantics and can be reviewed by considering the detailed explanation about infant formula approvals provided at the FDA website.[5]

The important concept in this process is that the FDA is fundamentally more empowered to assess safety than efficacy related to marketing of infant formulas. This is true

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whether they are small compositional changes or represent very different forms of key components such as protein. Infant formulas are regulated as food products, not as medications, and thus, are not subject to the same guidelines as medications for testing and evaluation. When components that are categorized by the FDA as "Generally Recognized as Safe" for infant use are added or varied, there is little the FDA can do to restrict their use. Furthermore, compositional variations or changes that fall within the guidelines of the IFA are unlikely to be blocked by the FDA. For example, small changes in protein, energy, or mineral amounts are at the discretion of the manufacturers as long as they meet the relatively broad ranges deemed acceptable in the IFA.

Where this issue becomes more confusing and even less transparent to consumers or pediatricians is when the form of a component is changed, such as when a different fat blend or mineral form is used in the formula. Again, whereas the public might imagine that each of these changes requires detailed laboratory, animal, and then human testing, this is not the case. It depends on the history of use of these components, the "Generally Recognized as Safe" status of the components for infant use, and the submission material provided by the manufacturer to the FDA to explain the changes. Simply put, such changes and variations are not always extensively tested before being released in the marketplace. Small scale metabolic and growth testing when available may be inadequate to assure safety when given to tens of thousands of infants and is likely to be inadequate to assure any unique benefit. Postmarketing surveillance is unlikely to be adequate to identify minor or unexpected problems with formulas and is subject to ascertainment bias.

Institute of Medicine Guidelines

Recognizing these problems, the Institute of Medicine (IOM) formed a committee specifically to make recommendations about the testing and evaluation of infant formulas. The IOM process led to the publication in 2004 of a very detailed document that includes recommendations related to in vitro, animal, and human studies that should be done prior to marketing new or significantly altered infant formulas. This remarkable document has never been implemented in the US, either voluntarily by manufacturer or by statute, nor does it appear to be used in a significant manner elsewhere in the world.[6] However, several recent suggestions have been made based on the IOM recommendations regarding ways in which preclinical testing might be improved for infant formulas.[7,8]

World Health Organization International Code of Marketing of Breast-Milk Substitutes

The aim of the World Health Organization (WHO) International Code of Marketing of Breast-Milk Substitutes is to provide for safe and adequate nutrition of infants worldwide through the protection and promotion of breastfeeding while ensuring that infant formulas (breast milk substitutes) are not inappropriately marketed. Further details of both the WHO Code as well as the Baby Friendly Hospital Initiative (also commonly referred to as the 10 Steps program) are beyond this discussion. However, several points are relevant. First, the WHO Code, originally published in 1981, has not been implemented in the US, the only country to originally vote against it.[9] Nor does the American Academy of Pediatrics (AAP) have a policy recommending it be followed. Of importance is that the Code does not permit direct advertising of infant formula to the public. Specifically, Article 5 states "There should be no advertising or other form of promotion to the general public of products within the scope of this Code."[10] Many other aspects of the code are often not followed in the US, as illustrated by the provision of free formula to health care workers. By following the WHO Code of Marketing of Breast-Milk Substitutes, along with the Baby Friendly Hospital Initiative to enhance health of infants through support of breastfeeding, many countries have greatly increased their breastfeeding rates.[11]

The Code clearly does not permit confusing mothers by marketing formulas as being equal or comparable with breast milk. This issue is very much in doubt in the marketing of breastfeeding "supplement" formulas as described below.[12] Even more important is that the accessibility through many media and online sources of direct marketing by companies of their products makes it difficult for pediatricians and other caregivers to guide families in their formula choices.

Other Guidance

Approximately one-half of infant formula in the US is distributed via the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) which is administered by the US Department of Agriculture (USDA). This is critical in that the WIC program must decide, on statewide and national levels, how new formulas should be handled based on their state contracts. As such, the WIC program and thus, the USDA is a key partner in evaluating formula changes in the US without a clear, pediatrician-directed process by which they evaluate these changes other than the infrequent overall review of WIC nutritional programming via the IOM. This recently became important when the WIC program (with variations in approach on a state-by-state basis) chose not to routinely allow the use of lower energy infant formulas without a medical request for the use of these formulas.

Specific Examples of Recent Formula Introduction Intended for Healthy Children and Possible Consequences of Their Marketing

Provided below is a discussion of several types of changes or novel formulas that have been introduced, or more widely marketed, in the last several years. In general, they are intended for healthy infants or those with relatively nonspecific symptoms such as mild-moderate colic or reflux.