

## How to tackle the problems of safety and quality of formula: examining effective measures

Powdered formulas are not sterile products and may become contaminated during the manufacturing process by harmful bacteria such as members of the *Enterobacter* family, for example *Enterobacter sakazakii*, and species of *Salmonella*.<sup>1</sup> The first problem is the severity of infections caused by these and other pathogenic bacteria which can cause invasive infection in newborns and infants because of the vulnerable stage of their development. Although infections such as meningitis, bacteraemia or necrotising enterocolitis (NEC) are rare, cases may be fatal or cause lasting neurological damage.<sup>2</sup>

The second problem is apparent under-reporting of *E. sakazakii*-related infections and those caused by other bacteria. Possibilities for testing are often limited, in particular in developing countries, by the scarcity or inadequacy of testing facilities. Under-reporting is therefore frequent « Globally there appear to be very few surveillance data for *E. sakazakii*-related illnesses. Although a couple of passive surveillance systems exist, no active surveillance system for *E. sakazakii*-caused diseases/conditions appears to exist. »<sup>3</sup>

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<sup>1</sup> *Enterobacter sakazakii* was reclassified in 2008 to regroup all the species that are pathogenic into a new genus, *Cronobacter*, but is still commonly referred to as *Enterobacter*.

See Note 3 for full references of FAO/WHO Reports on *Enterobacter sakazakii* and other microorganisms in powdered infant formula : <http://www.fao.org/food/food-safety-quality/a-z-index/enterobacter/en/>

<http://apps.who.int/bookorders/anglais/detart1.jsp?codlan=1&codcol=15&codcch=606>

<http://www.who.int/foodsafety/publications/micro/mra10/en/>

<sup>2</sup> Foodborne illness: *Cronobacter sakazakii* :

[http://www.foodborneillness.com/enterobacter\\_sakazakii\\_food\\_poisoning/](http://www.foodborneillness.com/enterobacter_sakazakii_food_poisoning/)

<http://www.foodpoisonjournal.com/cronobacter-sakazakii/#.Vs79y6TSmM8>

<sup>3</sup> See : World Health Organization report *Enterobacter sakazakii* in powdered follow-up formula, Executive Summary page xi :

[http://www.who.int/foodsafety/publications/mra\\_followup/en/](http://www.who.int/foodsafety/publications/mra_followup/en/)

The third and perhaps most disquieting problem is the emerging resistance of strains of bacteria such as members of the *Enterobacter* family to frequently-used antimicrobials (antibiotics), and more recently to the ‘antibiotics of last resort’ for treating serious infections in infants. « Available data on colonization with multi-drug resistant (MDR) *Enterobacteriaceae* in pediatric patients suggest that intestinal carriage of these organisms can last for months to years in some children. »<sup>4</sup>

**This article examines these problems further and then asks a series of questions, suggesting answers and solutions by assessing the arguments for and against each question: Why it is vital to ensure the safety and quality of formula? What measures are effective? Why have so few governments taken action to implement measures? What are formula manufacturers doing to stop contamination at factory level?**

## **1. Why it is so vital to ensure the safety and quality of formula.**

Formulas are industrially processed foodstuffs based on cows’ milk or soy; they therefore contain no live cells to protect infants against infections and boost the immune response. At birth, a baby’s immune system is immature and breastfed babies are protected by the anti-infective agents in breastmilk, a living fluid. These inhibit the growth of harmful bacteria and boost the maturation of the infant’s immune system. The article « Breastfeeding: maintaining an irreplaceable immunological resource » demonstrates the value that the anti-infective agents in breastmilk provide for the infant’s maturing immune system.<sup>5</sup> Research published in January 2016<sup>6</sup> revealed that « breastmilk contains an antibiotic capable of

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<sup>4</sup> See reports from the US Centers of Disease Control and Prevention :

<http://www.cdc.gov/HAI/organisms/cre/>

[http://wwwnc.cdc.gov/eid/article/21/11/15-0548\\_article](http://wwwnc.cdc.gov/eid/article/21/11/15-0548_article)

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4236051/>

<sup>5</sup> See <http://www.pubfacts.com/detail/15229475/Breastfeeding:-maintaining-an-irreplaceable-immunological-resource>

<sup>6</sup> See <http://www.sciencetimes.com/articles/8263/20160125/breastmilk-protein-eradicate-superbugs-study-reveals.htm>

treating drug-resistant bacteria. A protein medically known as lactoferrin keeps babies healthy in their first months, and could be effective in killing bacteria, viruses and fungi”, perhaps by sequestering the iron in breast milk so that it is not available for their use. The January 2016 Lancet series on breastfeeding emphasises that findings from studies done with modern biological techniques suggest novel mechanisms that characterise breastmilk as a personalised medicine for infants.<sup>7</sup>

Unlike breastfed infants, formula-fed infants do not benefit from these and many other types of protection against infections during the most vulnerable stages of their development. In addition, newborn infants are particularly at risk because « the stomach of newborns, especially of premature babies, is less acidic than that of adults : a possible important factor contributing to the survival of an infection with *Enterobacter sakazakii* in infants. » (See FAO/WHO Reports, ref. 1). Some babies are especially vulnerable: low-birth weight, immuno-compromised and premature infants, particularly those in Neonatal Intensive Care Units (NICUs). In an attempt to address some of the dangers of formula, some companies are experimenting with the addition of probiotics. However, when live probiotic micro-organisms are added to special formulas for pre-term or immuno-compromised infants, they may be contaminated by moulds that can cause fatalities.<sup>8</sup>

## **2. Which measures are effective? Resolutions, Recommendations, Guidelines or Guidance – or Legislation?**

### **2.1 World Health Assembly calls for explicit warnings**

Faced with this potential threat of powdered formula feeding for infant health, the Member States of the World Health Organization (WHO) discussed this matter twice, in 2005 and 2008. As a result, the World Health Assembly, WHA, the

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<sup>7</sup> Series papers: Breastfeeding: The Lancet ([www.thelancet.com/series/breastfeeding](http://www.thelancet.com/series/breastfeeding)). Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. Victora, Cesar G et al. The Lancet , Volume 387 , Issue 10017 , 475 – 490. Why invest, and what it will take to improve breastfeeding practices? Rollins, Nigel C et al. The Lancet , Volume 387 , Issue 10017 , 491 - 504

<sup>8</sup> See <http://www.formkit.com/news/2014-12-10-000000/fda-warning-dietary-supplements-containing-live-bacteria-or-yeast-pose-risk>

highest international policy setting body for public health, adopted two subsequent resolutions. The first resolution WHA 58.32 urged governments to ensure that health workers, parents and other caregivers are provided with information that powdered infant formula may contain pathogenic micro-organisms and must be prepared and used appropriately. The resolution included the exhortation to ensure « where appropriate, that this information is conveyed through an **explicit warning on packaging** (emphasis added). « The reason for this requirement is « the intrinsic contamination of powdered infant formula with *E. sakazakii* and *Salmonella* had been a cause of infection and illness, including severe disease in infants ... and could lead to serious developmental sequelae and death. »<sup>9</sup>

***! Major problem: Why still so few warnings on product labels and packaging?***

WHA resolutions are international health recommendations and do not have the force of a Treaty or Convention. Therefore, few governments have implemented the 2005 recommendation requiring manufacturers to provide information and label products with warnings about pathogenic micro-organisms. They have used the weasel words « where appropriate » and avoided taking action. Their explanation? « The companies argue that many consumers are unlikely to understand the term ‘pathogenic micro-organisms’ and feel using such a term might unduly scare them about product composition. «<sup>10</sup>

This is a spurious argument because it is perfectly possible to explain what these disease-causing bacteria are and the infections they may cause. Parents and others caring for infants, if they understand the reasons why, are capable of preparing formula correctly. This is, of course, unless they live in conditions of poverty which do not make it possible for them to take the extra care in preparing, storing and handling powdered formula. The real reason why manufacturers shy away from these crucial actions can be most likely interpreted as the fear of the loss of consumer confidence in their products if the facts are clearly stated – and a consequent dip in sales and loss of profits.

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<sup>9</sup> See Shubber S. The International Code of Marketing of Breastmilk Substitutes : History and Analysis. 2<sup>nd</sup> Edition 2011. Pinter and Martin Ltd.

<sup>10</sup> See 2016 edition of Action for Nutrition Index (ATNI), which provides information about companies so that potential investors can examine risks and assess profitability.

## 2.2 World Health Assembly calls for information and guidance

Three years later, in 2008, the second resolution WHA 61.29 adopted the Guidelines on safe preparation, storage and handling of powdered infant formula<sup>11</sup> which had been prepared by the WHO Secretariat to assist governments. WHA urged governments to take action to implement the WHO Guidelines. This tool includes the ‘lethal’ or ‘killer’ step to inactivate *Enterobacter* and *Salmonella* species, which are heat-resistant and are only inactivated or killed by high temperatures. Therefore, the Guidelines recommend that powdered formula should be prepared with very hot water, that has first been boiled and then cooled to no less than 70° C before adding the powder. Several governments have now issued national guidelines following the WHO recommendations. A list has been compiled and is being updated, as well as a list of product recalls and court cases<sup>12</sup>.

### ***! Major problem: shifting responsibility to individuals***

National guidance issued by these governments will hopefully prevent death and serious illness in babies. However, from the perspective of consumers, it removes responsibility from the formula manufacturers and places the onus of responsibility squarely on the product users – parents, care-givers and health professionals. If an infant or child falls ill due to contaminated formula, parents would most likely seek justice in a court room in vain. The company can argue that the formula was improperly prepared and stored and that safety precautions issued by the government were not followed.

In addition, formula manufacturers further fudge and shift the problem by arguing that handling very hot water at no less than 70°C presents a risk that those preparing powdered formula may scald themselves. This is a spurious and patronizing argument: is it really too risky for parents and health professionals to use boiling water, as they already do to prepare a cup of tea or coffee? The alternative to using really hot water to prepare powdered formula for an infant may entail serious infection or death.

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<sup>11</sup> See WHO : <http://www.who.int/foodsafety/publications/powdered-infant-formula/en/>

<sup>12</sup> See <http://ibfan.org/fact-contaminants-govt-action>

and <http://ibfan.org/fact-contaminants-reports-recall>

### 3. World Health Assembly calls for national regulation

The 2008 WHA resolution 61.29 also called for government action “through food safety measures, including appropriate regulatory measures, to reduce the risk of contamination of powdered infant formula and other pathogenic micro-organisms during the manufacturing process ... and to monitor the effectiveness of these measures”.

#### 3.1 Tackling the problem at factory level : Legislation by the US Federal Government

**This is the course taken by the US federal Government - and it required over 17 years.**

In July 2014 the US Food and Drug Administration( FDA) issued its Final Rule on Infant Formula: Current Good Manufacturing Practices (CGMPs); Quality Control Procedures; Notification Requirements; Records and Reports; and Quality Factors<sup>13</sup>. This document was issued as 3 separate legal texts. The final rule of July 15, 2014, « adopts, with some modifications, the interim final rule of February 10, 2014 » and the modifications of July 15, 2014. This process is explained in Note 1, while the history is explained in Note 2.

**For the purposes of this article, these 3 texts are called the Rule. The arguments in favour or against the Rule are analysed below as a series of Advantages and Disadvantages.**

#### 3.2 Purpose of the Rule

The Rule aims to « help prevent the manufacture of adulterated infant formula, ensure the safety of infant formula and ensure that the nutrients in infant formula are present in a form that is bioavailable ». The words « *and safe* » are added in the interim final rule but are not repeated in the final version of the rule. (See Note 1 for full texts of the interim and final Rule.)

**Most important**, the Rule concerns not only powdered formula but also liquid and other formulas for infants under 12 months of age.

**Equally important** is the fact that the Rule is a regulation under US federal law and is thus federally enforceable « The requirements in the final rule improve

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<sup>13</sup> For the pdf file see [www.gpo.gov/fdsys/pkg/FR-2014-06-10/pdf/2014-13384.pdf](http://www.gpo.gov/fdsys/pkg/FR-2014-06-10/pdf/2014-13384.pdf)

protection of infants consuming infant formula products by establishing greater regulatory control over the formulation and production of infant formula. » (See Interim final rule, legal authority in Note 1.)

**Advantages:** The sections of the Rule on safety and quality controls highlight the potential risks of formula feeding due to adulteration or contamination, and underscore the need to ensure that formula feeding is made safer for babies who are not breastfed. FDA uses the term adulteration of infant formula from microorganisms, rather than contamination, but the summary of the major provisions of Rule contains the crucial fact « Because powdered infant formulas are not sterile products, the interim final rule requires testing of representative samples of powdered infant formula at the final product stage, before distribution, and establishes values for two microorganisms, *Cronobacter* and *Salmonella* species (spp).  
«

**Disadvantages :** The above section is not re-stated in the final Rule, although this adopts the interim final rule with some modifications. The 3 versions of the Rule as published make comparisons complex and there is **no full final text of the Rule with a synthesis of the modifications and corrections.**

### 3.3 Scope of the Rule

According to the FDA Consumer Update of June 9, 2014, “FDA sets high quality standards for the safety and nutritional quality of infant formulas during this critical time of development”. The Rule therefore includes not only safety requirements for formula, but also its quality and nutritional adequacy. It thus “sets standards for:

- Current good manufacturing practices specifically designed for infant formula, including required testing for the harmful pathogens (disease-causing bacteria) *Salmonella* and *Cronobacter*.
- A requirement that manufacturers demonstrate that the infant formulas they produce support normal physical growth.
- A requirement that infant formulas be tested for nutrient content on three distinct occasions in the final product stage, before entering the market, and at the end of the products’ shelf life.”<sup>14</sup>

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<sup>14</sup> See ‘FDA takes Final Steps on Infant Formula Protections’ :

<http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm048694.htm>



**Advantages:** The scope includes not only powdered infant formula but also liquid infant formulas, either ready-to-feed or from concentrate as well as specific acidified foods. An infant is defined as under 12 months of age.

Apart from legally recognising the serious problem of adulteration, the Rule addresses both safety and quality of formula under the term ‘quality factors’, meaning “those factors necessary to demonstrate the safety of the infant formula and the bioavailability of its nutrients, as prepared for market and when fed as the sole source of nutrition, to ensure the healthy growth of infants.” The section on Definitions explains that it “modifies the wording of the definition of ‘quality factor’ in § 106.3 of the final rule. The revised definition still speaks to the safety of formula while clarifying that the term ‘bioavailability’ refers to nutrients.”

**Disadvantages:**

As explained in the FDA document quoted above, “The final rule applies only to infant formulas intended for use by healthy infants without unusual medical or dietary problems.” There are thus important exempt categories.

The FDA has therefore issued Draft Guidance for Industry on Exempt Infant Formula Production, listing the exemptions and containing recommendations on Current Good Manufacturing Practices, Quality Control Procedures, Conducts of Audits, and Records and Reports. **It is important to note that such Guidance documents contain only non-binding recommendations.**<sup>15</sup>

### **3.4 Nutritional adequacy of formula**

The Rule contains detailed provisions to address nutrient levels in infant formula and their bioavailability as well as sufficient biological quality of the protein used. It also specifies the date of November 12, 2015 for formula manufacturers to meet these requirements for quality factors in eligible formulas.

**Advantages:** Several provisions in the Rule require that infant formulas satisfy the two quality factors of normal physical growth and sufficient biological quality of the protein component of the formula. »<sup>16</sup> Section 106.96 lists the requirements

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<sup>15</sup><http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/InfantFormula/ucm384451.htm>

<sup>16</sup> FDA 2014 Guidance for Industry : Demonstration of quality factors requirements under CFR 106.96(i) :



for scientific evidence to demonstrate that a formula supports normal physical growth in infants for whom it is the sole source of nutrition. Furthermore, controls to prevent adulteration also address the problem of preventing nutrient deterioration by removing air from the finished product, ensuring proper sealing, instituting controls for stability and defining the length of shelf life (§ 105.50 2, 3, 4).

Disadvantages : As noted by George Kent in his article «“Regulating the Nutritional Adequacy of Infant Formula in the United States”<sup>17</sup> « The FDA lists safety issues of concern but does not speak in any systematic way about nutritional adequacy. The FDA offers no explanation of the importance of nutritional adequacy in all its dimensions. »<sup>18</sup>In an earlier article, “The Nutritional Adequacy of Infant Formula.”, Kent presents this concept of the role of formula in ensuring both physical growth in infants and also health outcomes: the child’s long-term health and development including not only physical growth but also protection against infections and allergies, and cognitive development. In the Rule « Attention to the role of growth has been carried over ... but the separate reference to health has been dropped. »

Kent provides a critique of the growth monitoring study required by the FDA (ref. 17) and notes that « if the FDA handles this the same way it handles safety assessments, it would accept the manufacturers’ analysis and conclusions and not form conclusions of its own. » **This underscores the major failing in the FDA Rule: the methods used to assess company compliance.**

### 3.5 Company Compliance

**There are in fact two important dates for compliance by formula manufacturers.** First, by September 8, 2014 manufacturers must comply with all provisions on controls to prevent adulteration or contamination of formula during

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<http://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/ucm400036.htm>

<sup>17</sup> Kent G. “Regulating the Nutritional Adequacy of Infant Formula in the United States.” Clinical Lactation, Vol. 5, No. 4, pp. 133-136 (2014).

<http://www.ingentaconnect.com/content/springer/clac/2014/00000005/00000004/art00006>

<sup>18</sup> In an earlier article, “The Nutritional Adequacy of Infant Formula.”, Kent presents this concept : see Clinical Lactation, Vol. 3, No. 1 (2012), pp. 21-25.

<http://www.ingentaconnect.com/content/springer/clac/2012/00000003/00000001/art00004>

processing and packaging. Then by November 12, 2015, manufacturers must comply with specific provisions on requirements for quality factors for formula and record-keeping<sup>19</sup>.

Although the Federal Register states « This final rule will set in place federally enforceable requirements for the safety and quality of infant formula», it is clear that the onus of responsibility lies with the manufacturers for controlling at every stage of the manufacturing and packaging process, and for end-product testing.

**Advantages:** Manufacturers cannot complain that they were not consulted and now must therefore comply with the provisions of the final rule and of the previous interim final rule; they were consulted extensively since 1996 and then further on both texts, as the FDA explains: “In light of comments received after the interim rule was published, the final rule provides some modifications and clarifications, and sets a date of September 8, 2014 for manufacturer compliance.” However, there appears to have been no process for in-depth consultations with civil society and product users and their comments were not registered.

**Disadvantages:** The provisions of the Rule include a plethora of provisions for controls and audit procedures. Each one begins with « A manufacturer », for instance « A manufacturer shall ensure, at any point, step or stage where control is necessary to prevent adulteration of infant formula, that all hardware is routinely inspected and checked according to written procedures ... »<sup>20</sup>

It is the manufacturers who must make and retain records of scheduled audits, but “although the findings shall be maintained they need not be made available to the FDA. »<sup>21</sup>

### ***! Who audits who – and how?***

**There appears to be a contradiction with earlier Guidance issued by the FDA for manufacturers, prompting the legitimate question: Does the 2014 federally enforceable Rule supersede the 2006 Guidance for Industry?**

In previous guidance documents, the FDA affirms that it “oversees manufacturers of infant formulas and helps ensure that these products are safe and support

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<sup>19</sup> See articles § 106.96(a), 106.96(b), 106.100(p)(2) and 106.100(q)(2) in Code of Federal Regulations (CFR) 21.

<sup>20</sup> Provisions in §§ 106.20 – 106.91 on Controls and §§ 106.100 on Records in the final rule.

<sup>21</sup> Provision § 106.100 (j).

healthy growth in infants who consume them.”<sup>22</sup> FDA explains that it “monitors infant formula products as part of its responsibility and conducts yearly inspections of all facilities that manufacture infant formula and collects and analyzes product samples. FDA also inspects new facilities. If FDA determines that an infant formula presents a risk to human health, the manufacturer of the formula must conduct a recall.” This FDA ‘oversight’ is not an approval system: “FDA does not approve infant formulas before they can be marketed. However, all formulas marketed in the United States must meet federal nutrient requirements, which are not changed by the new rule. Infant formula manufacturers are required to register with FDA and provide the agency with a notification prior to marketing a new formula.” (ref. 22)

**It is thus the manufacturers themselves which must notify the FDA of their own audits, control systems and record-keeping (§ 106.90-95). This is a notification system to the FDA and not an inspection system by the FDA.**

### **3.6 Testing for harmful microorganisms – but only for 2 of them**

The federally enforceable controls in the Rule thus « require testing of representative samples of powdered infant formulas at the final product stage, before distribution, and establish values for two microorganisms. » This testing is to be done by manufacturers for the species of two harmful pathogens (disease-causing bacteria) named *Cronobacter* spp. (the new name for *Enterobacter sakazakii*) and *Salmonella* spp. Both are well-known bacterial contaminants from fecal contamination; both can cause severe invasive infection in infants that can be life-threatening or lead to long-lasting neurological damage.<sup>23</sup>

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<sup>22</sup> <http://www.fda.gov/AboutFDA/Transparency/Basics/ucm336546.htm>

and « Is It really FDA Approved ? » : <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm047470.htm>

and « FDA Guidance for Industry » dated March 1, 2006:  
<http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/InfantFormula/ucm056524.htm>

<sup>23</sup> See Cronobacter Expanded Information by CDC :  
<http://www.cdc.gov/cronobacter/technical.html> and Cronobacter resources:  
<http://www.cdc.gov/cronobacter/resources.html>

The values for testing are given in § 106.55 on ‘Controls to prevent adulteration from microorganisms’: for *Cronobacter* spp. there must be none detected (0-zero) in 30 samples, with a sample size of 10 grams. For *Salmonella* spp. there must be none detected (0-zero) in 60 samples, with a sample size of 25 grams.

**Advantages**: The requirements listed in § 106.50 on Controls to prevent adulteration during manufacturing are detailed and comprehensive ; they include controls to prevent adulteration by workers, by facilities (water, ventilation, sanitation), by equipment or utensils, mechanical or electronic equipment, ingredients, containers or closures for the whole manufacturing process.

**Disadvantages**: Again it is the manufacturers who conduct the testing and there are no values for testing for other potentially harmful microbiological or fungal contaminants.<sup>24</sup> The text of the interim rule, subsequently adopted as the final rule, explains that “it had been tentatively determined to establish a standard for *Cronobacter* spp and *Salmonella* spp ... that manufacturers would be required to test representative samples of each production aggregate (batch) for the two pathogens; that testing for the five remaining microorganisms (fecal coliforms and *Listeria monocytogenes*, *Staphylococcus aureus*, *Bacillus cereus*) would not be required.” This is perplexing given the documented cases of contamination of formula and formula thickeners by *Bacillus cereus* and other spore-forming bacteria (see ref. 10). A court case was brought against the manufacturers of a formula thickener and testing showed that contamination by *Bacillus cereus* during manufacturing had caused severe and life-threatening Necrotizing Enterocolitis (NEC).<sup>25</sup>

## **! Manufacturers absolved of responsibility?**

**Does this mean that now that the Rule requires compliance by formula manufacturers, that they will report to the USFDA and therefore be able to state that they have complied with all regulatory requirements – and thus be relieved of any liability for their product causing severe invasive infection in formula-fed infants and young children, in particular those that are caused by other bacteria than *Cronobacter* spp and *Salmonella* spp?**

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<sup>24</sup> See the interim rule p. 7977

<sup>25</sup> <http://www.businesswire.com/news/home/20120502006598/en/York-Parent-Charges-SimplyThick-Infant-Food-Thickener>

and <http://www.courthousenews.com/2013/06/07/58315.htm>

### 3.7 Hygienic Practices, Storage and Record-keeping

Record-keeping of all quality-control procedures is key to identification of adulteration or alteration in bioavailability of nutrient levels in formulas.

**Advantages:** A comprehensive list of requirements for manufacturers is provided in Sub-part F, § 106.100 on Records.

**Disadvantages:** The Rule states in the earlier § 106.20 (i) « We are modifying the language to permit doors to toilet facilities to open into the plant facilities where infant formula, ingredients, containers or closures are processed, handled, or stored if alternate means have been taken to protect against contamination » These « alternate means » are however not specified.

Questions may also be asked about provision § 106.30 which was revised to read « A manufacturer may maintain a cold storage area for an in-process infant formula or for a final infant formula at a temperature not to exceed 45°F (7.2°C) for a defined period of time provided that the manufacturer has scientific data and other information to demonstrate that the time and temperature conditions of such storage are sufficient to ensure that there is no significant growth of microorganisms of public health significance during the period of storage of the in-process or final infant formula product ». **Once again, the onus is on the manufacturer to provide such evidence rather than on external verification.**

### 3.8 Discrepancies – inconsistency with other US Federal agencies

The preparation instructions for powdered formula given by the USFDA are quite different from those given by the US Centers of Disease Control and Prevention (CDC) <sup>26</sup>. Unlike the CDC documents, the FDA final rule mentions only once in the interim rule that powdered infant formula is not a sterile product, and of course omits the importance of the 'lethal' decontamination step in formula preparation to inactivate any harmful bacteria that may be present in the formula powder. In contrast, the CDC documents give clear instructions to mix the formula powder with water that has first been boiled and then cooled to not less than 70° C or 158° F before mixing the powder, to use the prepared formula

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<sup>26</sup> <http://www.cdc.gov/Features/Cronobacter/>

within 2 hours of preparation and to discard any formula if the baby does not finish the bottle « If in doubt, throw it out ».

### 3.9 Recall Requirements

Earlier documents dating from 2006 (ref. 22) state the « FDA is authorized to initiate an FDA-mandatory recall if the agency determines that an adulterated or misbranded infant formula presents a risk to human health. » However, the Rule in § 106.100 stipulates « When there is a reasonable possibility of a causal relationship between the consumption of an infant formula and an infant's death, the manufacturer shall, within 15 days of receiving such information, conduct an investigation and notify the Agency (FDA) as required in 106.50.» Is there a discrepancy between these documents or is it a case of a distinction between probable or definite causality?

Regarding recalls, the Rule in § 106.70 states « Any rejected infant formula shall be clearly identified as having been rejected for use and shall be controlled under a quarantine system designed to prevent its release or distribution. »

***! Will this rejection include repackaging for redistribution or dumping in Third Countries of products that do not meet USFDA regulatory requirements?***

## 4. Conclusion

As a U.S. Federal Government Ruling, the Rule was published in the Federal Register of the Code of Federal Regulations (CFR). It is thus federally enforceable and became effective as of July 15, 2014. As noted by Kent (op.cit.), the FDA is « the federal agency with primary responsibility for ensuring the quality of infant formula » Thus « This agency's standards are important not only for people living in the U.S. but also for people elsewhere. Other national governments may assume that the standards set in the U.S. are sound and adopt its methods. »

**The Government of Bangladesh did not wait for the U.S. to finalise their texts.** On May 14, 2014 the Government issued Act No. 35 of 2013<sup>27</sup> as an Act to re-enact and repeal the 1984 Ordinance on the Regulation of Marketing. Whereas the U.S. Rule has no provisions for punishment or fines for non-compliance by manufacturers, the law in Bangladesh imposes Penalties : « 12(2) If a child becomes ill or dies from the use of any breast-milk substitutes, infant foods, commercially

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<sup>27</sup> Issued as an Act to re-enact and repeal the 1984 Ordinance on the Regulation of Marketing of Breast-milk Substitutes, Infant Foods, Commercially Manufactured Complementary Foods and the Accessories Thereof.

manufactured complementary foods or of any accessories thereof, it shall constitute a punishable offence under this Act, and for that the company that has produced (these products) shall be punished with 10 (ten) years of imprisonment or with a fine which may extend to maximum fifty lacs or with both, and the fine so imposed shall be given in the prescribed manner to the family of the victim. »

It remains to be seen how the Bangladeshi law will be enforced; the by-laws in preparation in 2015 will address more specific issues of bacterial contamination. The law and its by-laws will apply to all parents whose babies have suffered, and not only to those who can afford expensive court cases, as occurs in the United States.

Given the severity of infection and the long-lasting disabilities caused by contaminated powdered infant formulas, it is not only imperative to enact laws and regulations, but also to enforce them and penalise manufacturing companies which fail in their obligations to protect the health and safety of vulnerable infants.

It is not sufficient for manufacturers to conduct their own testing, their own reports and audits. It is not enough for them to make them available to the FDA. The testing must be independent and result must be made available to the public. Manufacturers must be held accountable; in the Courthouse reviews (ref. 25), the parents of the baby who suffered catastrophic injuries say it all « There are no words to explain how much suffering this has caused our little girl and how much despair and hopelessness we as her family have endured » The attorney for the family has the final word « Infant food manufacturers owe a duty to parents and babies to prepare and sell safe products. »

### **Note 1. Regulatory Status: Legal Texts**

In 2014 the Rule was published in the Federal Register of the Code of Federal Regulations (CFR) Parts 106 and 107 under section 412 of the Federal Food, Drug and Cosmetic (FD&C) Act, under and the Infant Formula Act of 1980 passed by Congress, which amended the FD&C Act to include this section 412. In 1986, Congress amended Section 412 under the Anti-Drug Abuse Act, to address ‘concerns related to the sufficiency of quality control testing, current good manufacturing practice, recordkeeping, and recall requirements for infant formula.’



(See Purpose of the Interim Final Rule and Summary of Legal Authority, page 7934 of the Federal Register.)

### **The Final Rule is made up of three texts:**

- The **first** is the text of the interim final rule, published in the U.S. Federal Register of February 10, 2014.<sup>28</sup> This first text contains all the articles: <https://www.federalregister.gov/articles/2014/02/10/2014-02148/current-good-manufacturing-practices-quality-control-procedures-quality-factors-notification>
- The **second** is the text of the final rule published in the Federal Register of June 10, 2014. This text includes only the modifications made to the interim final rule after comments were received. The Summary explains « This final rule affirms the interim final rule's changes to FDA's regulations and provides additional modifications and clarifications. The final rule also responds to certain comments submitted in response to the request for comment on the interim final rule. » See: <https://www.federalregister.gov/articles/2014/06/10/2014-13384/current-good-manufacturing-practices-quality-control-procedures-quality-factors-notification> For the pdf file : [www.gpo.gov/fdsys/pkg/FR-2014-06-10/pdf/2014-13384.pdf](http://www.gpo.gov/fdsys/pkg/FR-2014-06-10/pdf/2014-13384.pdf)
- The **third** text contains corrections to « some errors that appeared in the Preamble of the final rule » and was published in the Federal Register of July 15, 2014, thus making the 3 texts effective as July 15, 2014: <https://www.federalregister.gov/articles/2014/07/15/2014-16476/current-good-manufacturing-practices-quality-control-procedures-quality-factors-notification>

### **Note 2. History of the Rule and Background:**

The process of finalising the Rule lasted 17 years, with 8 actions between 1996 and November 2013. These actions for review and comments by manufacturers are related to the sufficiency of quality control testing, current good manufacturing practices (CGMP), record-keeping, and recall requirements for infant formula. The comments on the interim final rule show how hard the companies fought at

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<sup>28</sup> See also the Announcement of the interim final rule on February 6, 2014 : <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm384886.htm>

every stage. These comments and the responses are available online.<sup>29</sup>

<https://www.federalregister.gov/articles/2014/02/10/2014-02148/current-good-manufacturing-practices-quality-control-procedures-quality-factors-notification>

### **Note 3. Details of FAO/WHO references:**

World Health Organization (WHO) and Food and Agriculture Organization (FAO) Microbiological Risk Assessment Series (MRA) No. 6 Meeting Report 2004 : *Enterobacter sakazakii* and other microorganisms in powdered infant formula :

<http://apps.who.int/bookorders/anglais/detart1.jsp?codlan=1&codcol=15&codech=606>

World Health Organization (WHO) and Food and Agriculture Organization (FAO) Microbiological Risk Assessment Series (MRA) No. 10 Meeting Report 2006 : *Enterobacter sakazakii* and *Salmonella* in powdered infant formula :

<http://www.who.int/foodsafety/publications/micro/mra10/en/>

World Health Organization (WHO) and Food and Agriculture Organization (FAO) Microbiological Risk Assessment Series (MRA) No. 15 Meeting Report 2008 : *Enterobacter sakazakii* and other microorganisms in powdered infant formula :

<http://www.fao.org/food/food-safety-quality/a-z-index/enterobacter/en/>

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<sup>29</sup> See <https://www.federalregister.gov/articles/2014/02/10/2014-02148/current-good-manufacturing-practices-quality-control-procedures-quality-factors-notification>