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Good Questions 5. How can a food product be both old and new?

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Abstract

How can some foods and food additives be regarded as novel and subject to patent claims and at the same time be *obviously* safe? In dealing with its responsibilities to ensure the safety of foods, it looks like the U.S. Food and Drug Administration (FDA) acts in ways that favor the manufacturers and expose consumers to unnecessary risk.

The FDA uses the term GRAS, Generally Regarded as Safe, to identify products as not requiring further study to establish their safety. Any person may "notify" the FDA that a product is GRAS. The FDA does not accept or agree with the notifier's GRAS conclusion. Usually the FDA simply does not question the notifier's claim.

This approach to "regulation" is illustrated through examination of Evolve BioSystems' trademarked product, Evivo, claimed to be "the first and only probiotic powder clinically proven to restore the infant gut microbiome to its original, natural state."

Evivo is obviously a new and unfamiliar product. It is only because it is novel that Evolve Biosystems pursued patents relating to it. The FDA's primary responsibility is to protect public health. The FDA's refusing to accept a GRAS claim by a manufacturer would not be an assertion that it the product is unsafe. It would simply be an assertion that, as a matter of prudence, its safety should be investigated by an objective agency both before and after it is marketed. That is not too much to ask, especially when the consumers are highly vulnerable children.

Good questions

How can some foods and food additives be regarded as novel and eligible for patent claims and at the same time be *obviously* safe? In dealing with its responsibilities to ensure the safety of foods for infants and young children, it looks like the U.S. Food and Drug Administration (FDA) acts in ways that favor the manufacturers and expose children to unnecessary risk.

GRAS

The FDA uses the term GRAS, Generally Regarded as Safe, to identify products as not requiring further study to establish their safety:

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> The Food and Drug Administration (FDA or we) is issuing a final rule that amends and clarifies the criteria in our regulations for when the use of a substance in food for humans or animals is not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) because the substance is generally recognized as safe (GRAS) under the conditions of its intended use. We also are amending our regulations to replace the voluntary GRAS affirmation petition process with a voluntary notification procedure under which any person may notify us of a conclusion that a substance is GRAS under the conditions of its intended use. The clarified criteria for GRAS status should help stakeholders draw more informed conclusions about whether the intended conditions of use of a substance in food for humans or animals complies with the FD&C Act, and the notification procedure will enable stakeholders to be aware of whether we have questioned the basis of a conclusion of GRAS. (Food and Drug Administration 2016a)

The FDA itself does not decide whether a food product is GRAS. Any person may "notify" FDA that a product is GRAS. When that happens . . .

> In general, FDA's response has been in one of three categories:

1. The agency does not question the basis for the notifier's GRAS conclusion;

2. The agency concludes that the notice does not provide a sufficient basis for a GRAS conclusion (e.g., because the notice does not include appropriate data and information or because the available data and information raise questions about the safety of the notified substance); or

3. The response letter states that the agency has, at the notifier's request, ceased to evaluate the GRAS notice. (Food and Drug Administration 2016b)

Notably, option 1 does not say FDA accepts or agrees with the notifier's GRAS conclusion. It says only that the FDA does not question it.

Probiotics

The Evolve BioSystems company announced a new trademarked product:

> Evivo (activated *B.infantis* EVC001-ActiBif®) is the first and only probiotic powder clinically proven to restore the infant gut microbiome to its original, natural state. Evivo is a probiotic powder that is mixed with breast milk and fed to babies each day to help release nutrients in breast milk and create a protective internal environment in baby's gut. It also helps develop baby's immune system, and builds the foundation for lifelong health. (Evolve BioSystems 2018a)

By scrolling down on this website and clicking on Learn More, and then scrolling down again and clicking on Shop Now, one learns that the product can be purchased from the company online for US$80 a month.

Evolve Biosystems says deficiencies in breast milk can be remedied through the administration of Evivo to infants by mixing small amounts of the powder with the mother's expressed breastmilk. It has not yet been shown whether this procedure is actually likely to lead to improved health outcomes later in the infant's life.

Is there a need to "restore the infant gut microbiome to its original, natural state"? David Kyle of Evolve Biosystems is quoted as saying Evivo would help "lower the pH of the infant microbiome down to where it used to be in the US 100 years ago, or what you might find in the developing world today" (Watson 2018a; also see Underwood et al. 2014).

Breastmilk adapts to local conditions (Holmlund et al. 2010). Why should people in high-income countries with good sanitation and environmental conditions emulate the body conditions of people in low-income countries?

The reasoning here is not easy to follow. Things change. How do we know that the change is not some sort of positive adaptation, one that we don't yet understand? We are used to seeing claims that there is something missing in infant formula and needs to be added (e.g., Chu 2018; Daniells 2018; DuPont 2018a; also see Kay 2018). But claiming there are important and widespread deficiencies in most women's breastmilk is new and questionable. An Internet advertisement for Evivo and also its website at https://www.evivo.com/?utm_source=Amazon&utm_medium=display&utm_campaign=science&utm_term=OM) claim " 90% of babies lack *B. infantis*, the key good bacteria that digests special nutrients in breast milk and protects baby's gut."

Where did they get this bit of information? Is this their way of suggesting to women that they don't need a diagnosis; they just need the Evivo remedy?

This claim should alarm health professionals and breastfeeding advocates everywhere. Suggesting that there is a serious deficiency in most women's breastmilk is a very serious matter, not to be taken lightly. If infants don't get important beneficial bacteria from their mothers, and this needs to be remedied, why haven't pediatricians around the world and UNICEF and the World Health Organization raised their voices about this? Should companies be free to alarm the public like this, and offer remedies at the same time, without intervention by any governing or regulatory body?

For women who are not convinced by the company's claim that 90 percent of women have the problem and want to have their own individual diagnosis, the company offers a convenient kit with which each woman could make her own diagnosis (Watson 2018c).

Evivo is to be sold in high-come countries to "restore" infants' gut bacteria to the condition that prevails in low-income countries. What argument did they use to get $40 million in funding for promoting the product in Asia, to "help infants suffering from severe acute malnutrition (SAM) through the restoration of the gut microbiome"? (Evolve Biosystems 2018b)

A study to assess Evivo measured some of the impacts of giving it to breastfed infants from day 7 to day 28 (Frese et al. 2017). It was published in *mSphere*, the journal of the American Society for Microbiology. Several of the co-authors are with Evolve Biosystems and participated in Evolve Biosystems patent applications (Justia Patents 2017; United States Patent Application 2017). The paper was received by *mSphere* on October 24, 2017 and accepted for publication 15 days later, 6 days shorter than the journal website says is its average. The journal requires substantial payment from authors of papers they publish ($3300 for non-members). On its Frequently Asked Questions (FAQ) page, the journal admits that standards for publication in mSphere are not very high:

> The ASM already publishes mBio®. How is mSphere different?
> mBio has a very high standard for acceptance, and many important and significant studies cannot be accommodated by mBio. Such studies may have a home in mSphere. (https://msphere.asm.org/content/faq)

The recommendation for using this product is based on the claim that it will help develop the effective functioning of infants' immune systems. What studies have been done to show it actually does that? What studies will be done after it is on the market to assess whether it does in fact improve children's health over the long term? A sophisticated approach to assessing supplements proposed to accompany breastfeeding is provided by the Academy of Breastfeeding Medicine (Taylor and the Academy of Breastfeeding Medicine 2018).

The Evolve Biosystems website describes the deficiency as possibly due to modern birthing practices, especially the use of cesarean delivery. However, on their FAQ page, Evolve Biosystems addressed the question, "Does it matter if my baby was born vaginally or via cesarean?" They answered:

> Not at all. Regardless of delivery method, most moms today don't have the right bacteria to pass on to their babies. Evivo is activated *B.infantis* and works with breast milk to restore the infant gut microbiome to its original, natural state. (Evolve Biosystems 2018c)

This answer raises another question: How do they know this deficiency is a problem for "most moms"? Who has surveyed what populations to reach this conclusion? How was the problem diagnosed for whole populations? Have there been any broad population-based studies to confirm that there is such a deficiency? Do we really know whether it has serious consequences? More importantly, what studies have demonstrated that using Evivo actually improves infant health?

To the question, "What is the regulatory approval process for Evivo," Evolve Biosystems said:

> Evivo is a food, first and foremost and is an important component in the efficient and complete use of breast milk for newborn infants.
>
> Within the FDA, the Office of Food Additive Safety oversees a process called GRAS status for many types of products, including Evivo. These products must complete an extensive process of scientific and data review by independent qualified experts, who assess whether the product is safe under the conditions of its intended use. Evivo gained GRAS status for use with term infants after successfully completing this process, with consensus by all independent qualified experts. (Evolve Biosystems 2018c)

Why is it described as a food and not as a medication that would require a prescription following diagnosis by a pediatrician? One reason might be that it is easier to sell the product as a food. Less obviously, the FDA is concerned only about the safety of foods, while for medications, the FDA is concerned with safety and effectiveness. Evolve Biosystems offers little scientific evidence to support its claims regarding its effectiveness. Since it has been called a food, that does not matter to the FDA.

The GRAS assessment of the safety of this food is questionable. As explained above, the FDA asks the manufacturer whether the product safe to use. Evolve Biosystems said Evivo gained

GRAS status after successfully completing a GRAS review process. How can anyone conclude that a new product used in a new way is safe when it has no history? The idea that the Evivo product is new and not an already a well-known food, is clearly indicated by Evolve Biosystems' patent application.

There are similar issues with other products, especially additives to infant formula. Another example is Ganeden's probiotic product (Menayang 2017).

In the DuPont example referenced above, DuPont was pleased to announce that its product had obtained GRAS status:

> DuPont Nutrition & Health has received a 'No Objection' letter for its Care4U 2´-fucosyllactose (2'-FL), a human milk oligosaccharide (HMO), aimed at narrowing the nutritional gap between breast milk and formula. (Daniells 2018)

The company also mentioned that it had gained European Union approval as a novel food at the start of 2018. They did not point out that the European Union says, "Novel food is defined as a food that had not been consumed to a significant degree by humans in the EU before 15 May 1997. . . (European Commission). If it had not been consumed, how could it have gotten GRAS status in the U.S?

In a comparable case, Martek promoted the addition of certain fatty acids to infant formula. The additive provided little benefit and increased the cost of infant formula to the families. There was no obvious basis for the GRAS determination for the new fatty acid additive developed by Martek (Kent 2014).

Another example of questionable GRAS determination came up in the history of soy-based infant formula. As I pointed out elsewhere:

> Soymilk has been categorized as GRAS because historically soybeans have been used in the human diet in many forms with no major problems. That categorization was carried over to soy-based infant formula even though there had been no prior experience with using soymilk as practically the entire diet, whether for adults or for infants. . . . . It is irresponsible for the FDA to simply accept that soy-based infant formula is known to be safe and does not require studies of its safety. Soy is widely accepted as part of the diet for adults, but one should not assume it is for that reason safe to use as the basis for the entire diet of infants. (Kent 2011, 25)

Conclusions

There has been a long history of innovation in foods for infants and young children, sometimes exposing them to risks while providing little or no benefit. The products may be presented to the public as something new, and novelty is an important element in applications for patents. But when they want gentle treatment by a regulatory agency, it is more useful to claim it is an old and familiar product. There are firms devoted to helping manufacturers make their case for

obtaining GRAS status with the FDA, such as Dicentra in Toronto, Canada (https://gras.dicentra.com/).

Food expert Marion Nestle's critical assessment is relevant here:

> The GRAS exemption was initially created to cover ingredients that are widely known to be safe, such as vegetable oil, but has been applied in recent practice to novel chemicals and is now a loophole that has swallowed the law. (Nestle 2017; also see Lehner 2017; Watson 2012)

The problem of failure to ensure the safety of novel foods applies not only to children's foods but to many other types as well (Starks 2017). Here is an example.:

> As there is no history of widespread consumption of leghemoglobin from the roots of the soybean plant, said the FDA, Impossible Foods based its safety arguments on its structural and functional equivalence to other widely consumed globin proteins, arguing that heme B-containing globin proteins "have been safely consumed throughout human history". (Watson 2018b)

This obfuscation by a manufacturer is disgraceful. It is far worse when it is accepted by a governmental agency whose primary responsibility is to protect public health. The FDA's refusing to accept a GRAS claim by a manufacturer would not be an assertion that it the product is unsafe. It would simply be an assertion that, as a matter of prudence, the safety of this product should be investigated by a reasonably objective agency both before and after it is marketed.

Government regulatory agencies should be more interested in protecting public health than private wealth. In managing risks, they should follow the Precautionary Principles that have guided many agencies for many years (Lougheed 2009).

How can applying for a patent and also asking for GRAS status make sense? When the risks are borne by infants and young children, the most vulnerable segments of any population, the highest priority should be to ensure that their interests are protected. This can only be done if experts are provided who can speak in behalf of infants' interests. Just as a *guardian ad litem* can be called on to represent a child's interests in a courtroom, in the regulation of foods for children, there is a need for involvement of experts who can speak effectively on behalf of all infants and young children. That does not happen in the FDA's GRAS process.

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