

Mind the Gap – Identifying Language Barriers between Translational Science and Regulators

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Abstract

Objectives: Human milk, the gold standard for infant nutrition, is a complex system and a limitless source of innovation. Advances in discovery science have expanded knowledge of how nutrition impacts infant development, while breakthrough technologies in food manufacturing have produced isolated or biosimilar milk ingredients with the potential to bring the composition of infant formula closer to human milk. However, questions about the safe inclusion of these ingredients remain. This poster explores the gap between translational science and regulatory frameworks using two case studies: recombinant human lactoferrin (rhLF) and isolated bovine osteopontin (bOPN). While these bioactive milk proteins hold promise for improving infant nutrition, their safety evaluation processes highlight critical language barriers between scientific discovery and regulatory interpretation. **Methods:** Materials from the U.S. Food and Drug Administration (FDA) Freedom of Information Act (FOIA) Reading Room, including GRAS Notifications, notifier communications, internal memorandums, and referenced publications, were reviewed for (a) expert scientific opinion and (b) questions from regulatory officials. **Results:** A key challenge lies in the differing lexicons of researchers and regulators. Scientific literature often emphasizes mechanisms of action, biomolecular interactions, and translational potential, whereas regulatory agencies prioritize risk assessment and establishment of standards. For rhLF, concerns over structural equivalency, allergenicity, and manufacturing consistency complicated regulatory acceptance, while isolated bOPN encountered scrutiny regarding its compositional comparison to human milk OPN and potential immunogenic effects. **Conclusions:** These case studies underscore the necessity of clearer communication strategies to facilitate regulatory approval. Misalignment in terminology, data expectations, and frameworks often results in prolonged review periods and scientific misunderstandings. Opportunities to align regulatory, industry, and academic scientists are needed to ultimately advance infant nutrition.

Case Study 1: Lactoferrin

Background

Human lactoferrin from bioengineered sources has a history in the U.S. FDA GRAS program. In the mid 2000's three GRAS submissions were notified to FDA (U.S. FDA, 2007, 2005, 2004)¹⁻³. Despite GRAS panel agreement that both forms of hLF (produced by transgenic rice and transgenic cows) were safe, FDA ceased to evaluate all three notices. In 2022, through the Freedom of Information Act (FOIA), FDA released more than 1100 pages of correspondence between the agency and these companies. In the released documentation FDA highlighted key gaps in the GRAS notices submitted by each company. Paraphrased unanswered safety questions from FOIA specific to hLF from bioengineered sources are shown below. An early stage biotech startup producing recombinant hLF (Helaina) prepared a safety study framework to address historical scientific gaps, including the lack of published data⁴. It follows the recommendations of two expert panels that evaluated the risk assessment of human proteins, such as lactoferrin, in food, as outlined below.

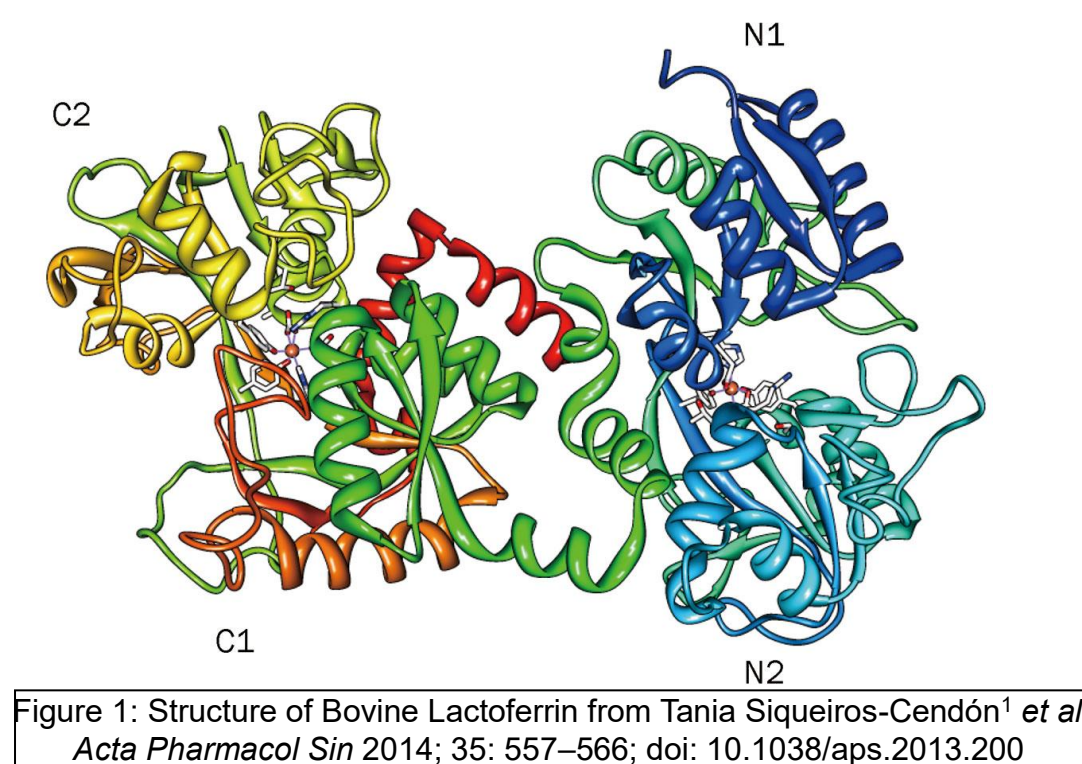
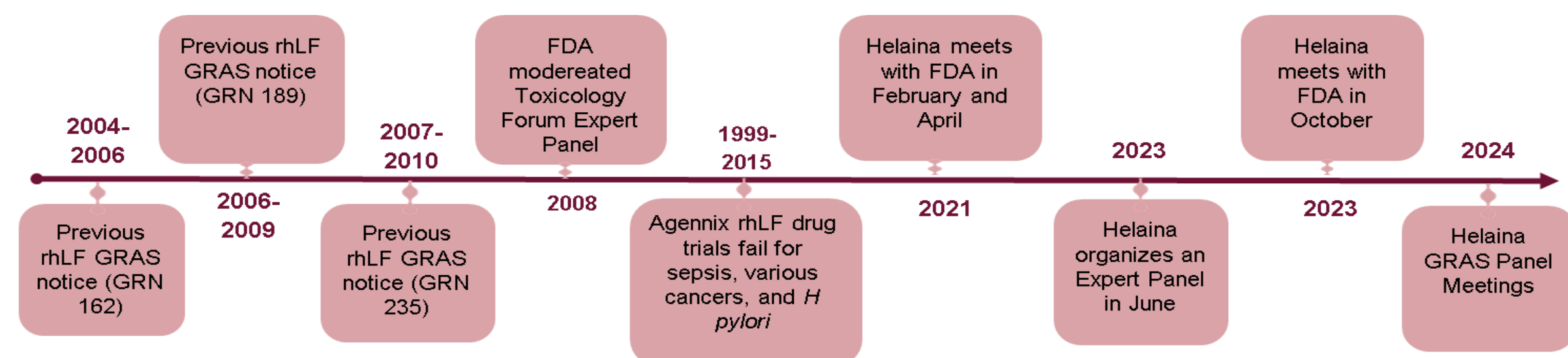


Figure 1: Structure of Bovine Lactoferrin from Tania Siqueiros-Cendón et al. Acta Pharmacol Sin 2014; 35: 557-566. doi: 10.1038/aps.2013.200

Timeline of key events



Case Study 2: Osteopontin

Background

Osteopontin (OPN) is found at much higher concentrations in human milk than in bovine milk⁵. Evidence suggests that early-life intake of OPN supports immune, intestinal, and neural development⁶. In 2022, the European Food Safety Authority (EFSA) concluded that bovine milk-derived OPN (bmOPN) is safe for addition to infant formula (0–6 months), follow-on formula (6–12 months), and young child formula (1–3 years) at concentrations up to 151 mg/L⁷. Although EFSA acknowledged inconsistencies and limitations in the scientific evidence, they did not consider them safety concerns. In contrast, FDA did not accept the GRAS Notice 716⁸ for bmOPN, which was withdrawn in 2018 after unresolved safety concerns. Internal FDA documents detail key issues (FDA, 2020), including: variability in dietary exposure to human milk OPN; justification for the proposed bmOPN levels in formula; absence of absorption, distribution, metabolism, and excretion (ADME) data; potential to cross the blood–brain barrier; long-term immunomodulatory effects and mechanisms; functional similarity to human milk OPN; limitations of standard toxicological methods; and possible links to immune-related diseases. These differing regulatory perspectives highlight ongoing scientific and safety questions regarding bmOPN in infant nutrition.

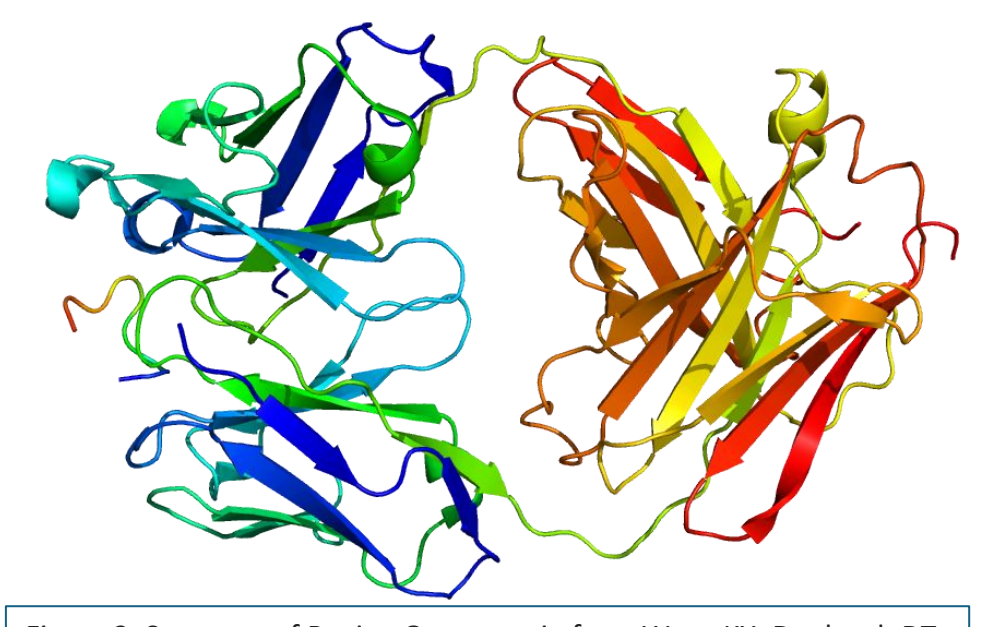
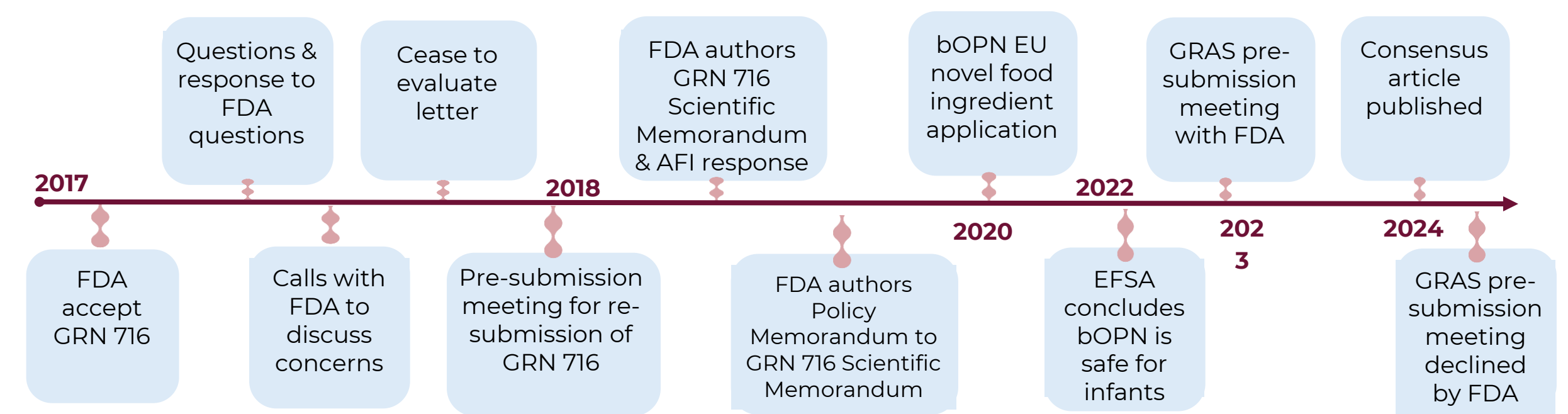


Figure 2: Structure of Bovine Osteopontin from Wang KX, Denhardt DT. Cytokine Growth Factor Rev. 2008;19(5-6):333-345. doi:10.1016/j.cytogfr.2008.08.001

Timeline of key events



Regulatory Requirements

In the U.S., the FDA conducts a pre-market evaluation of infant formula products to ensure all ingredients are safe and suitable for use in infant formula; that is, a substance is used in accordance with the Agency's food additive regulations, **is generally recognized as safe (GRAS)** for such use, or is authorized by a prior sanction (21CFR106.40).

The safety standard for food additives (21CFR170.3) and GRAS (21CFR170.30) ingredients is that there must be an established reasonable certainty of no harm of the ingredient under the intended conditions of use.

In addition, the safety of GRAS ingredients must be:

- **Generally accepted among qualified experts**, and
- Established using **generally available data**

Table 1: Preclinical and Clinical Studies to Address Immune Safety Questions of Alloimmunity/Immunogenicity, Immunotoxicity, and ADME of rhLF and bOPN

Study	Redbook Rec	Alloimmunity/immunogenicity		Immunotoxicity		ADME	
		rhLF	bOPN	rhLF	bOPN	rhLF	bOPN
Allergenicity assessment (FARRP)		√	√				
Pepsin digestion		√	√				
In vitro adult digestion (INFOGEST)		√	√			√	√
14-d DRF rat study	√			√	√		
28-d rat study	√	√	√	√	√	√	√
Dendritic cell study		√					
PBMC study		√					
T-cell analysis		√					
Human clinical study		√	√				

√ = the safety question/s being addressed in each study; ADME = absorption, distribution, metabolism, and excretion; rhLF = recombinant human lactoferrin; bOPN = bovine osteopontin; FARRP = Food Allergy Research and Resource Program (University of Nebraska, US); DRF = dose-range-finding; PBMC = peripheral blood mononuclear cell

Unanswered Safety Questions

Unanswered Safety Questions from human LF FOIA

1. **Immunogenicity (Alloimmunization) /Allergenicity/Autoimmunity:** Does ingestion of rhLF lead to a breakdown in tolerance?
2. **Immunotoxicity:** Does ingestion of rhLF lead to immunotoxicity?
3. **Iron homeostasis:** How does ingestion of rhLF affect iron homeostasis?
4. **ADME:** What are the differences in digestion between hmLF and rhLF produced from transgenic sources

Unanswered Safety Questions from OPN FOIA

1. Functional role of hOPN in breastmilk
2. Significance of variability of hOPN levels in breastmilk
3. Functional differences and similarities between hOPN and bOPN Evidence of bioequivalence
4. bOPN and hOPN post-translational and peptide processing in vivo and differences in OPN's processing
5. Scientific understanding of bOPN's biological effects and modes of action in the infant body
6. Immediate and long-term effects of bOPN on infant's maturing immune system
7. OPN's immunomodulatory and proinflammatory properties
8. Safety endpoints for bOPN
9. Need for a long-term, on-going, and robust debate among different scientific and medical disciplines
10. Public symposium with appropriate pediatric experts to critically evaluate existing data and confirm safety
11. Peer-review and publication of expert meeting results

Conclusion

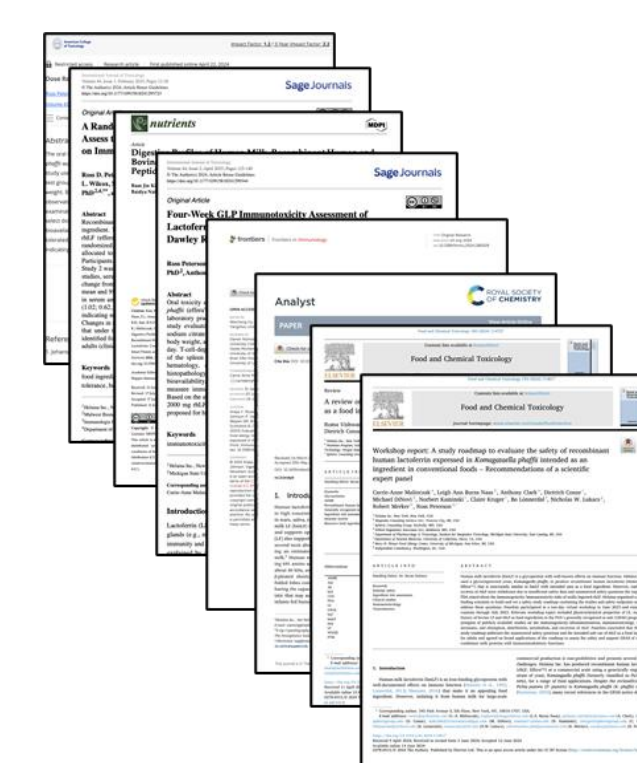


Figure 3. Scientific publications in response to FDA feedback

Despite numerous attempts at bringing novel ingredients into infant formula, with companies tailoring their safety plan to outstanding safety questions from FDA, FDA still wants **additional consensus and expert feedback on the science**

References

1. FDA. (2004) GRN 162
2. FDA. (2005) GRN 189
3. FDA. (2007) GRN 235
4. Malinczak, C. A. et al., 2024 doi:10.1016/j.fct.2024.114817
5. Schack, L., et al., 2009 doi:10.3168/jds.2009-2360
6. Demmelmair, H., et al., 2017 doi:10.3390/nu9080817
7. Turck, D., et al., 2022 doi:10.2903/j.efsa.2022.7137
8. FDA. (2017) GRN 716

How to Drive Consensus

The Infant Nutrition Science Coalition (INSC) brings together experts from academia, government, and industry to advance research on human milk and infant nutrition. The INSC is focused on **driving consensus** in areas where scientific evidence, regulatory perspectives, and industry practices intersect. By fostering collaboration, the INSC works to align methods, measures, and terminology to strengthen the scientific foundation for infant nutrition. Through this work, the INSC supports clearer communication, stronger science, and safer, more effective infant feeding options.

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