Role of 100% Whey Protein Partially Hydrolyzed in Infant Formula & Reducing the Risk of Allergy in Healthy Infants

Rationale and Substantiation for a Qualified Health Claim
The Standard

- Nutritionally
- Functionally
Historically, formulas have evolved to make cow’s milk nutritionally and functionally closer to human milk.
Pathogenesis and Prevention of Allergic Disease

Genetics + Environment + Allergens → Sensitization → Tolerance → Allergy

Primary Prevention: Prevention of Sensitization

Treatment

Skin
Intestinal
Respiratory
Food Allergies: 90% accounted for by 5 foods

5 most common allergens in infants:
- Cow Milk
- Soy
- Wheat
- Peanuts/Tree nuts
- Egg

Cow milk protein:
- the most common food antigen in infants
- the most common protein used in infant formulas
Protein Size and Allergic Reactions

Intact Proteins

Hydrolyzed Proteins

Processing by the Intestinal Immune System

Chance for Allergic Reaction
Hydrolysis Can Reduce Allergenicity of Cow Milk Proteins

Median Molecular Weight of Infant Formulas

<table>
<thead>
<tr>
<th></th>
<th>Daltons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensively Hydrolyzed Casein</td>
<td>450</td>
</tr>
<tr>
<td>Partially Hydrolyzed Whey</td>
<td>1,100</td>
</tr>
<tr>
<td>Whole Protein Casein/Whey</td>
<td>10,000</td>
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</tbody>
</table>
100% Whey Protein Partially Hydrolyzed
To Reduce the Risk of Allergy

• Strong theoretical basis
• Controlled clinical trials
  – 18 Published clinical trial reports (various ages)
  – 12 independent patient cohorts
  – Varying size, design, significance, quality
  – Most done in infants with a family history of allergy
• All showed a reduction in incidence of atopic disease
Cumulative Incidence of Atopic Manifestations < 12 months of age
100% Whey Protein Partially Hydrolyzed Formula vs Cow Milk Formula in Prevention Studies

* Graph depicts only published, peer-reviewed, prospective trials with data collection at timepoints ≤12 months.
** For all studies except Becker 2004, AM includes AD as one of the allergic outcomes assessed; for Becker 2004, AM refers to asthma alone.
**** p-values in italics indicate that no p-value is reported in publication; p-value is based on calculated OR and CI
Cumulative Incidence of Atopic Dermatitis < 12 months of age

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Cumulative Incidence of Allergic Manifestations > 12 mo of Age

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- p-values in italics indicate that no p-value is reported in publication; p-value is based on calculated OR and 95% CI
- Chan 2002 not included. Wheezing reported exclusively, not inclusive of other AM at 30 months.
The German Infant Nutritional Intervention (GINI) Study

- Independent, government-sponsored study
- 2,252 healthy infants with history of allergy in the family randomized at birth to:
  - Intact cow milk formula vs three hydrolysates
- When not exclusively breast fed, randomized formula was given to 6 mo of age, infants followed up to 12mo
- Incidence of allergic manifestation at 12 months was 13%
  - 89% of all allergic manifestation was atopic dermatitis
- 12 month results published, 3-year publication pending,

Cumulative Incidence of Atopic Dermatitis

- Intact Cow Milk
- Partially Hydrolyzed Whey
- Extensively Hydrolyzed Whey
- Extensively Hydrolyzed Casein

Absolute cumulative incidence shown.
Meta-Analysis: Formulas containing hydrolysed protein for prevention of allergy


- Inclusion criteria
  - Randomized trials comparing use of hydrolyzed infant formula to human milk or CMF
  - ≥ 80% follow-up of subjects
  - 18 / 72 studies were eligible for inclusion
Cochrane Meta-Analysis Conclusions

“In high risk infants [infants with a positive family history of allergy], who are unable to be completely breast-fed, there is evidence that prolonged feeding with a hydrolysed, compared to cow’s milk formula reduces infant and childhood allergy and infant [cow’s milk allergy].”

“Further trials are required to determine if significant clinical benefits persist beyond five years of age and if there is any additional benefit from use of an extensively compared to a partially hydrolysed formula. Incremental costs of formula and the effect on compliance should be measured.”

100% Whey-Protein Partially Hydrolyzed Formula

• Routine use formula
• Palatability comparable to intact protein formulas
• Cost comparable to other brand name routine formulas
• Why is this important?
Effective Risk Reduction

- Routine use, wide availability
- Acceptable, affordable
- Benefits the population at large
## Prevalence of atopic disease based on parental history

<table>
<thead>
<tr>
<th>Prevalence of Parental Atopic History</th>
<th>64% No Parental Hx</th>
<th>31% Uniparental</th>
<th>5% Biparental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Prevalence of Atopic Disease</td>
<td>(10-15%)</td>
<td>(20-30%)</td>
<td>(30-40%)</td>
</tr>
</tbody>
</table>

**Total:** 17.6%  
**Prevalence:** 9.6%  

**Other refs:**  
Prevalence of Parental Atopic History: 64% 31% 5%

Prevalence of Atopic Disease in German Infants (total 17.6%): 9.6% 6.4% 1.6%

> 50% of children who develop allergy do not have a family history

Most infants at risk for atopy go unidentified
Prevalence of Parental Atopic History: 64% 31% 5%

Prevalence of Atopic Disease in German Infants (total 17.6%): 9.6% 6.4% 1.6%

> 50% of children who develop allergy do not have a family history

For those who have a family history, there is no mandatory, standardized nor validated mechanism or tool to elicit parental history

Most infants at risk for atopy go unidentified
In Summary: 100% Whey-Protein Partially Hydrolyzed Formulas

- Well documented role in reduction of the risk of allergy associated to use of intact cow milk protein
- Applicable to the general population
- Safe, Acceptable, Affordable strategy
Proposed Claim

“Breastfeeding is the best way to nourish infants. For infants who are not exclusively breastfed, emerging clinical research in healthy infants with family history of allergy shows that feeding a 100% Whey-Protein Partially Hydrolyzed formula may reduce the risk of common food allergy symptoms, particularly allergic skin rash, when used instead of whole-protein cow’s-milk formula from the initiation of formula feeding.

Partially hydrolyzed formulas are not intended to treat existing food allergy symptoms. If you suspect your baby is already allergic to milk, or if your baby is on a special formula for the treatment of allergy, your baby's care should be under a doctor's supervision.”
100% Whey Protein Partially Hydrolyzed: The Latest Generation In Infant Formulas

- Raw Cow Milk
- Processed Whole Cows Milk
- “Casein Predominant” Formula
- “Formula” with Evaporated Cow Milk
- “Whey Predominant” Formula
- “100% Whey Protein Partially Hydrolyzed” Formula

100% Whey Protein Partially Hydrolyzed: The Latest Generation In Infant Formulas
Addenda:
Additional Allergy Background
Allergy

• Affects as many as 50 million Americans
• Occurs in up to 30% in some populations
  – particularly developed countries
• Leading cause of chronic disease in the U.S.
  – overall - allergies are on the rise
• Food allergy - most common in infants and children
Trends in Atopic Dermatitis Prevalence

*Secular trends in the UK
Eichenfield et al., 2003 Pediatrics 111: 608-16
Atopic Dermatitis: Significance

- Atopic dermatitis in the U.S.
  - Prevalence 10-20% overall†
  - Affects 15 million Americans‡
  - 17% prevalence by 6 months of age*
  - 7 million visits per year ‡

- Up to 60% of children with severe atopic dermatitis have food hypersensitivity**

† NIH- HHS Publication No. 03-4272, Rev April 2003
‡ CDC Nat Ctr for Health Statistics Vital and Health Statistics Series, 1996, 13:134
* Moore MM - Pediatrics - 01-MAR-2004; 113(3 Pt 1): 468-74
Allergic March

• Atopic dermatitis may be the first step in the Allergic March: the relationship between allergic manifestations throughout life

  – Approximately 75-80% of atopic dermatitis patients develop allergic rhinitis
  – More than 50% of atopic dermatitis patients develop asthma

Spergel J Allergy Clin Immunology 2003; 112 (6 Suppl): S 118-27
Increasing Prevalence of Asthma and Atopy

Ninan et al., 1992; BMJ 304: 873-75