Peptides to Stimulate Cell Metabolism & Connective Tissue and for Protein Enrichment

Training II
Martin Walter, Jessica Pföhler, Stephan Hausmanns
GELITA at a glance.

- **Legal Form:** GELITA is an independent, unlisted stock company owned by the founding families.
- **Founding Year:** 1875
- **Headquarters:** Eberbach, Germany
- **Turnover:** ~ 600 Mio. €
- **Production Plants:** 18
- **Sales Offices:** 4
- **Market Share:** ~ 26% (Market Leader)
- **Employees:** ~ 2,600
Our locations are part of our philosophy: we are there where we are needed.
Our global business unit structure – three strong pillars to serve various customer demands.

**Business Unit**

- **Gelatine**
  - Food, Pharma, Photo, Technical

- **Collagen Peptides**
  - Health & Nutrition, Medical

- **Fats, Proteins, Minerals**
  - Food, Pet Food, Technical

*FPM Ingredients*
Collagen Properties are Based on Molecular Structure

Collagen structure:
Right handed triple alpha chain super helical with a length of ~300 nm and a diameter of 1.5 nm
Each chain is a sequence of 1014 AS with left-handed helix conformation

Biological role of Collagen: Adding stability to life
• Collagen fibrils having the tensile strength of steel
• Main component of connective tissue
• Up to 35% of the whole-body protein content
• Up to 70% of dry cartilage mass
• Also abundant in bone, skin, ligaments, tendons, blood vessels and intervertebral disc.
• Accounting for 6% of the weight of strong, tendinous muscles
# Functional Properties of Collagen Proteins

<table>
<thead>
<tr>
<th>Features</th>
<th>Collagen</th>
<th>Gelatine</th>
<th>Collagen Peptides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gelling &amp; thickening</td>
<td>firm gel – short texture</td>
<td>firm to soft gel – elastic texture</td>
<td>no gel</td>
</tr>
<tr>
<td>Thermo-reversible gel-formation</td>
<td>Yes</td>
<td>Yes</td>
<td>--</td>
</tr>
<tr>
<td>Water binding</td>
<td>excellent</td>
<td>very good</td>
<td>--</td>
</tr>
<tr>
<td>Solubility</td>
<td>Partially in warm water</td>
<td>Completely in warm water</td>
<td>Completely in cold water</td>
</tr>
<tr>
<td>Buffer capacity</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Emulsifying &amp; foaming</td>
<td>good</td>
<td>very good</td>
<td>medium</td>
</tr>
<tr>
<td>Film-forming properties</td>
<td>medium</td>
<td>very good</td>
<td>good</td>
</tr>
<tr>
<td>Cohesiveness/adhesiveness</td>
<td>very good</td>
<td>very good</td>
<td>very good</td>
</tr>
<tr>
<td>Compatibility in food systems</td>
<td>very good</td>
<td>very good</td>
<td>very good</td>
</tr>
</tbody>
</table>
# Health & Nutrition Related Aspects of Collagen Proteins

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Collagen</th>
<th>Gelatine</th>
<th>Collagen Peptides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergenic potential</td>
<td>virtually zero</td>
<td>virtually zero</td>
<td>virtually zero</td>
</tr>
<tr>
<td>Digestibility/bioavailability</td>
<td>good</td>
<td>very good</td>
<td>excellent</td>
</tr>
<tr>
<td>Calorie management</td>
<td>water binding</td>
<td>water binding</td>
<td>fat reduction</td>
</tr>
<tr>
<td></td>
<td>fat reduction</td>
<td>fat reduction</td>
<td>sugar reduction</td>
</tr>
<tr>
<td></td>
<td>fat replacement</td>
<td>(Active satiety increase)</td>
<td>protein enrichment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Active satiety increase)</td>
</tr>
<tr>
<td>Joint health</td>
<td>--</td>
<td>--</td>
<td>cartilage recovery</td>
</tr>
<tr>
<td>Bone health</td>
<td>--</td>
<td>--</td>
<td>bone structure</td>
</tr>
<tr>
<td>Beauty</td>
<td>--</td>
<td>--</td>
<td>skin health, hair, nails</td>
</tr>
</tbody>
</table>
Collagen Amino Acid Composition
Differentiation of Collagen, Gelatine and Collagen Peptides

- Improving indulgence, convenience and nutritional properties
- Stimulating body function, measurable health improvement

Collagen

- Water-in-water systems
- Emulsified systems
- Texturizing and immobilization of water

Gelatine

- Foamed systems
- Emulsified systems
- Texturizing and immobilization of water

Collagen Peptides

- Skin health
- Cartilage regeneration
- Improving bone structure
- Improving indulgence, convenience and nutritional properties
- Stimulating body function, measurable health improvement
Specific Bioactive Collagen Peptides® to Optimize Stimulation of Certain Body Functions

Collogen → Hot water extraction → BCP 1 (VERISOL®) → Optimized stimulation of fibroblasts in skin

Specific Enzymes

BCP 2 (FORTIGEL®) → Optimized stimulation of chondrocytes in joint cartilage

Specific Enzymes

BCP 3 (FORTIBONE®) → Optimized stimulation of osteoblasts in bones

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Branded Products behind the Science

- Bioactive collagen peptides scientifically proven to stimulate growth of connective tissue, collagen & proteoglycans synthesis in particular
  - FORTIGEL® improves joint health
  - Effective dose: 5.0 g/day
Specific **Bioactive Collagen Peptide® to Stimulate Condrocytes**

- A special composition of natural *Bioactive Collagen Peptides®* (e.g. FORTIGEL®) obtained by special enzymatic degradation of collagen (mean M.W. 3.3 kDa), optimized to protect and rebuild joint cartilage
- Scientifically validated in numerous international pre-clinical and clinical studies (over 3,000 patients)
Historical Background

The Nutritional Therapy of Saint Hildegard of Bingen (1098 – 1179)

„He who has stabbing pain in his limbs and joints as well as stomach and intestinal pain, should frequently eat plenty of well-cooked beef trotters, including fat and calluses. That soon gets rid of the pain.“

Paris, National Library, Cod. 6952
“Collagen glue” can Contribute to Rebuild and Maintain Collagen Structures and could cause an Increase in Collagen Mass
Healthy Joint Cartilage

Catabolism  Anabolism

Extra Cellular Matrix

Proteases

Collagen (Type II)

Proteoglycan (Aggrecan)

Chondrocyte
Cartilage Degeneration
Bioactive Collagen Peptides® Stimulating Collagen Production
Mode of Action using the Example of Cartilage

Composition of Joint Cartilage

~ 25% Proteoglycans
~ 70% Collagen
Cells (Misc.)

FORTIGEL® (Specific Bioactive Collagen Peptide®)

Stimulation
Production
Regeneration

Increase of Cartilage Mass
FORTIGEL® Pre-Clinical Research Path

Rapidly absorbed, partially in intact form

Distribution & accumulation in target organ

Stimulation of chondrocytes
FORTIGEL® Pre-Clinical Research Path

- **Rapidly absorbed**, partially in intact form
  
  Distribution & accumulation in target organ

- Stimulation of chondrocytes

- Excellent and rapid absorption of collagen peptides after oral uptake (Iwai et al. 2005)

- Significant and continuous increase of collagen-specific amino acids in human blood after collagen peptide supplementation (Beuker et al. 1993)
FORTIGEL® Pre-Clinical Research Path

Rapidly absorbed, partially in intact form

Distribution & accumulation in target organ

Stimulation of chondrocytes
FORTIGEL® Pre-Clinical Research Path

Rapidly absorbed, partially in intact form

Distribution & accumulation in target organ

Stimulation of chondrocytes

Accumulation of SCP peptides in cartilage tissue

Radioactivity in cartilage (Bq/g tissue)

Time [h]

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FORTIGEL® Pre-Clinical Research Path

Rapidly absorbed, partially in intact form

Distribution & accumulation in target organ

Stimulation of chondrocytes

Dose-dependent stimulation of type II collagen biosynthesis

FORTIGEL® stimulates collagen\(^1\) and proteoglycan\(^2\) biosynthesis

2) Osser S et al. (2005) Osteoarthr Cartilage 13: Suppl. 152
# FORTIGEL® Clinical Scientific Substantiation

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Published</th>
<th>Subjects</th>
<th>Study design</th>
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<tbody>
<tr>
<td>Krug</td>
<td>1979</td>
<td>193</td>
<td>open</td>
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<td>Götz</td>
<td>1982</td>
<td>60</td>
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<tr>
<td>Oberschelp</td>
<td>1985</td>
<td>154</td>
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<td>Seeligmüller</td>
<td>1989</td>
<td>356</td>
<td>open</td>
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<tr>
<td>Adam</td>
<td>1991</td>
<td>81</td>
<td>double-blind, placebo controlled, randomized, crossover</td>
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<tr>
<td>Seeligmüller</td>
<td>1993</td>
<td>519</td>
<td>open</td>
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<tr>
<td>Beuker, Eck</td>
<td>1996</td>
<td>40</td>
<td>open</td>
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<tr>
<td>Beuker, Rosenfeld</td>
<td>1996</td>
<td>100</td>
<td>double-blind, placebo controlled, randomized</td>
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<tr>
<td>Moskowitz</td>
<td>2000</td>
<td>389</td>
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<td>Rippe</td>
<td>2004</td>
<td>250</td>
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<tr>
<td>Rippe</td>
<td>2005</td>
<td>102</td>
<td>double-blind, placebo controlled, randomized</td>
</tr>
<tr>
<td>Flechsenhar, Alf</td>
<td>2005</td>
<td>100</td>
<td>open</td>
</tr>
<tr>
<td>Clark</td>
<td>2008</td>
<td>147</td>
<td>double-blind, placebo controlled, randomized</td>
</tr>
<tr>
<td>McAlindon</td>
<td>2009</td>
<td>30</td>
<td>double-blind, placebo controlled, randomized</td>
</tr>
</tbody>
</table>
Harvard University / Tufts Medical Center Study (2011) Visualized the Joint Health Effect of FORTIGEL®

Design:
• Prospective, randomized, double blind, placebo controlled
• 30 individuals with mild grade of Osteoarthritis (Kellgrean grade 1 – 2)
• Therapy: 10 g FORTIGEL® or placebo
• 11 months trial
• dGEMRIC data

Results
• Proteoglycan density in the knee joint cartilage was significantly increased after FORTIGEL® treatment

* FORTIGEL®
NOCA Observational Study 5g FORTIGEL®
2011/2012

Design
- Observational study coordinated by NOCA
- Conducted in Germany – 2011/2012
- Random recruitment of patients coming to the doctor’s office (orthopedist)
- Study group
  - 20 patients
  - with mild / moderate osteoarthritis in knees and hips
  - 50% female / 50% male
  - Age 63 +/- 10
  - BMI 27.4 +/- 3.4
  - Daily use of 5g FORTIGEL® - provided in a 10g sachet
Summary and Conclusion

- Results confirm that same effects as with 10g/day of FORTIGEL® can be achieved. These effects have been demonstrated by a growing body of scientific studies.

- A FORTIGEL® dose of 5g/day showed significant effects.
- Proof of concept.
Evolution in Joint Care Therapy

**FIRST GENERATION**

- **Pain killers and anti-inflammatory medicine:**
  - Addressed symptoms and some short term relief and improved mobility

**SECOND GENERATION**

- **Chondroitin and Glucosamine:**
  - Anti-inflammatory effect and pain relief
  - Suggested to stimulate proteoglycan synthesis

**THIRD GENERATION**

- **FORTIGEL®**
  - Evidence of collagen AND proteoglycan synthesis, exerting an effect on total cartilage mass
  - Counteracting causes AND symptoms of cartilage degeneration
  - Improving physical performance & mobility

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Collagen Peptides for Regeneration of Connective Tissue
Exemplary Products in the Market
Branded Products behind the Science

• Bioactive collagen peptides scientifically proven to stimulate growth of connective tissue, collagen & proteoglycans synthesis in particular
  • VERISOL® improves skin health (Beauty-from-insight)
    • Effective dose: 2.5 g/day
Why VERISOL® Beauty-From-Within Matters:

- Mainly occurring in the dermis, Collagen is the major structural component of skin, comprising about 80% of dry skin weight. Collagen mainly influences skins water binding capacity, elasticity and outside appearance (wrinkles).

- Loss of Collagen starts with the age of ~ 30 and significantly increase after menopause (2% p.a.*).

VERISOL® Collagen Peptides (CP) - Mode of Action

- Rapidly absorbed, partially in intact form
- Distribution & accumulation in target organ
- Stimulation of fibroblasts

Stimulation of Extracellular Matrix Molecules in Human Skin Cells by VERISOL® Treatment
Clinical Studies 1 & 2 (2011, 2012)

VERISOL® Significantly Increases Elasticity, Hydration & Collagen Concentration in Skin and Reduces Wrinkles

Design Study 1:
• Randomized, placebo-controlled, blinded
• Participants: >60 women, age 35-55
  Supplementation: VERISOL® oral dosage 2.5 & 5 g per day vs. placebo
• Test period 8 weeks
• Cutaneous aging parameter: Skin elasticity (Primary Outcome)

Design Study 2:
• Randomized, placebo-controlled, blinded
• Participants: >110 women, age 35-55
  Supplementation: VERISOL® oral dosage 2.5 per day vs. placebo
• Test period 8 weeks
• Cutaneous aging parameter: Wrinkle Volume (Primary Outcome)
VERISOL® Clinical Studies at Department of Dermatology, SIT Hamburg - Design

Study I
- Randomized, placebo-controlled, blinded observational
- Participants: >60 women, age 35-55 years, normal skin
- Supplementation: Hydrolyzed collagen (VERISOL®) oral dosage 2.5 & 5 g per day vs. placebo
- Test period 8 weeks, measurement after 4 & 8 weeks, 4 weeks wash out
- Cutaneous aging parameter:
  - Skin elasticity (Primary Outcome)
  - Further skin related parameter (Secondary Outcome)

Study II
- Randomized, placebo-controlled, double-blinded clinical study
- 114 women (57 per group), age 55.6 ± 5.7
  8 drop outs (not treatment related)
  7 subjects reported discomfort (2 VERISOL®, 5 placebo)** - flatulence, stomach ache or pyrosis
- Supplementation: Hydrolyzed collagen (VERISOL®) 2.5g vs. placebo
- Daily intake of one sachet over 8 weeks
- Test period 8 weeks, measurement after 4 & 8 weeks, 4 weeks wash out
- Evaluate the efficacy of a VERISOL® treatment on eye wrinkle reduction
VERISOL® Clinical Study: Results

• Both VERISOL supplemented groups showed significantly higher skin elasticity compared to placebo after 4 & 8 weeks (p < 0.01)

• No significant difference between different VERISOL dosages or differences in other skin parameters
VERISOL® Clinical Study: Sub-group analysis

- Skin elasticity significantly increased with a daily dosage of already 2.5 g and clearly more pronounced in women (≥ 50 years).
VERISOL® Clinical Study: Sub-group analysis

- Increased hydration of skin (11-14 %) and lower skin evaporation (6-7 %) in women > 50.
- Moisturizing effect suggests that VERISOL® treatment improves epidermal barrier regeneration and matrix synthesis of dermal proteoglycans in aged skin.
Eye Wrinkle Assessment
Wrinkle Depth - Comparison to Baseline

p < 0.05 vs. baseline

VeriSol
Placebo

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CONFIDENTIAL! GELITA proprietary data
Eye Wrinkle Assessment
Pro-Collagen Accumulation – Comparison to Baseline

Pro-collagen Accumulation in sub epidermal fluid [rel. to baseline]

- **Verisol**
  - Baseline: 1.0
  - End of treatment: 1.8
  - p = 0.013

- **Placebo**
  - Baseline: 1.1
  - End of treatment: 1.2
  - n.s.

p = 0.028

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VeriSol – Study (EFSA II) Eye Wrinkle Assessment

Tropo-Elastin Accumulation - Comparison to Baseline

Mann-Whitney U-Test; n = 20

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VeriSol – Study (EFSA II) Eye Wrinkle Assessment

ECM Accumulation - Comparison to Baseline

Mann-Whitney U-Test; n = 20

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VERISOL® Study II: Exemplary Study Results

VERISOL®, Baseline vs. 8 week treatment, and Placebo, Baseline vs. 8 week treatment.
VERISOL® Clinical Studies - Conclusion

• Oral administration of 2.5 g / day VERISOL® improves skin elasticity, reduces wrinkle depth and increases dermal pro-collagen and elastine concentration significantly after 4 weeks and leads to higher skin tightness and improved epidermal barrier regeneration

• VERISOL® positively influences epidermal and dermal skin structures and thus counteracts skin-aging and improves skin appearance.
Market Research Proves Market Potential for VERISOL®

- Quantitative survey with 1,500 women aged 20-65 in DE, FR & ES (2011)
- Qualitative survey in DE, ES, USA (2011/2012) on the basis of 6 focus groups
- Lessons learned, e.g.:
  - The term “Collagen” is associated with “Beauty” by 80% of target group.
  - “Beauty From Within” is considered to be more effective than topical measures as it works in a systemic manner.
  - Requirements: Natural product, no negative side effects.
VERISOL®: Close to Unlimited Applicability

- VERISOL® is a clean label food ingredient with high bioavailability
- Suitable for manifold applications
  - Daily dose only 2.5g
  - Excellent & clearly soluble in warm & cold water
  - pH and temperature resistant
  - Superior sensorial profile, almost neutral in taste

- Renewable raw materials, high sustainability

* Low polyphenol concentration required
Safety, IP & EU Regulatory Status

- VERISOL® is food. It is safe to use in all food applications and show no allergenic potential (mammalian derived).
- Natural Protein Reg. (EC) No 853/2004
- FDA GRAS status (Docket Number 77N-0232).
- Patents:
  - WO 2012/065782: Collagen Hydrolysate used to improve the health of human skin, hair and/or nail.
  - DE-Patent Publication, unpublished: VERISOL® as bioactive ingredient to act against Cellulites
- EFSA Article 13.5 Health Claim filed
- Article 8 Nutrition Content Claim “Contains Collagen” already possible.
Exemplary Market Products

- ProPharma, Ukraine
- Blackmores, Australia
- Snella, Brazil
- Vinamilk, Vietnam
- IHS / Merck, Germany
- Medex, Slovenia
- Probiótica Laboratories, Brazil
- Qyra, Gelita, Germany
Bone Health – An Outlook

Bone structure
- 10% water
- 70% anorganic minerals
- 20% organic material from which collagen type 1 is 95%


A diet rich in specific collagen peptides together with CA-sources causes a higher bone collagen metabolism

Ongoing clinical research!
FORTIBONE®

- Stimulates biosynthesis of bone extracellular matrix (framework for calcium). A diet rich in specific collagen peptides together with calcium-sources causes a higher bone collagen metabolism
- Down-regulates degenerative mechanisms
- Improves bone stability and flexibility
- Supports bone density
- Clinical studies ongoing

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PETAGILE®

Specifically designed to keep animals mobile & active

**Elderly animals**
- regain mobility
- well-being
- enjoy life without pain

**Active animals**
- prevent joint discomfort
- increase performance

**Clinical data available and research ongoing**
IP Established

- Confidential Production Know-How
- Trademarks, Regional & IR, Classes 5 (+ 1, 29, 31, 32 in selected countries)
  - FORTIGEL®, VERISOL®, FORTIBONE®, PETAGILE®, BIOACTIVE COLLAGEN PEPTIDES®
- Patents:
  - EP 0 777 491 B: Use of tasteless collagen hydrolysate and agent containing the same.
  - WO 2011/149596: Composition for treating degenerative joint disease
  - WO 2012/065782: Collagen Hydrolysate used to improve the heath of human skin, hair and/or nail.
  - Unpublished: Composition for nutritional use
  - Unpublished: Cellulites
- EFSA Proprietary Data Protection Applied for Article 13(5) FORTIGEL® and VERISOL® Health Claim Dossier

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Collagen hydrolysates (peptides) are food and natural proteins (clean label). They are safe to use in all food applications without restriction and show no allergenic potential (mammalian derived).

- **FDA GRAS status (Docket Number 77N-0232).**
- **Nutrition label:** Collagen Hydrolysate or Gelatin Hydrolysate
- **EFSA Article 8 Nutrition Content Claim** “Contains Collagen” possible.
- **EFSA Article 13.1 Health Claim** FORTIGEL® rejected in 2011

**EFSA Article 13.5 Heath Claim**

- “FORTIGEL”: 0297_DE - Art 13.5 Claim, Reg.(EC) No 1924/2006, "Collagen Peptide Mixture (Collagen Hydrolysate)" has a beneficial physiological effect on the maintenance of joint health in physically active people (rejected)
- “VERISOL” M-2012-0279 EFSA-Q-2012-00839 0366_DE - Art 13.5 Claim, Reg.(EC) No 1924/2006, Collagen hydrolysate, and, maintenance of skin health (evaluation ongoing)
Collagen Peptides: “Essential Improvement” of Up-to-Date Protein Formulas and Blends

- Natural protein (Reg. (EC) No 853/2004)
  - Food (Clean label; no Food additive)
  - Zero allergic potential (mammalian derived)
  - High bioavailability
- Suitable for manifold applications
  - Excellent & clearly soluble
  - Neutral in taste
  - Broad range of resulting viscosities
  - High water binding capacity
- Renewable raw materials, high sustainability
Thank you!

Join us at # F32