

Hemina Skin Rebuilding and Reconditioning Therapy: Treating Ichthyosis & Xerosis

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Purpose

- To design a moisturizing package that treats ichthyosis skin disorder and xerosis (dry skin)
- May target other skin disorders



Agenda

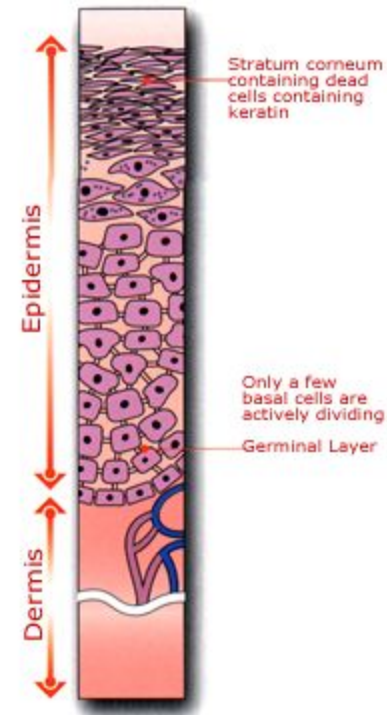
- Anatomy
- The Skin Disorder
- Treatment
- Our Original Product
- Substitutes and Modeling Consumer Attitudes
- Demand Model
- Manufacturing
- Economic Analysis



Anatomy

The Human Skin

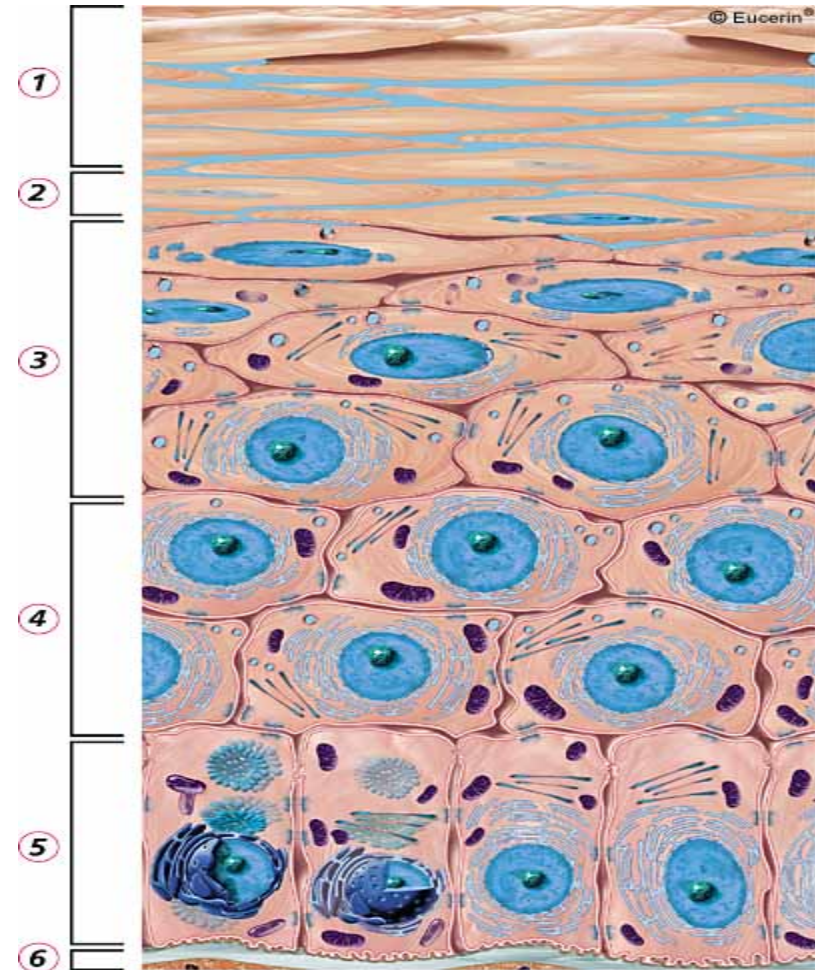
- Self-contained organ that exists as a semipermeable barrier layer
- Two components with interdependent functions: epidermis and dermis



Source: www.healthzone.co.uk

Epidermis

- ~40 μm thick
- Four (or five) layers
 1. Stratum corneum
 2. (Stratum lucidum)
 3. Stratum granulosum
 4. Stratum spinosum
 5. Stratum basale
- Basal membrane (6)



Source: www.eucerim.co.uk



Stratum Corneum

- Generally ~10-15 μm thick
- Tough but pliable quality given by keratin
- 10–20 layers of corneocytes embedded in a matrix of lamellar lipids

Stratum Corneum

- “Brick and mortar” structure

- Corneocytes (bricks)

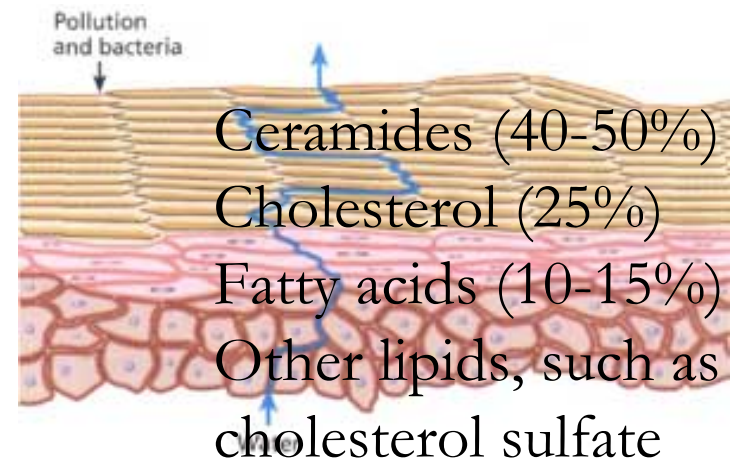
- Anucleated, non-viable, keratin-rich cells

- Hydrophilic

- Lipid lamellae (mortar)

- Tight lateral packing

- Hydrophobic



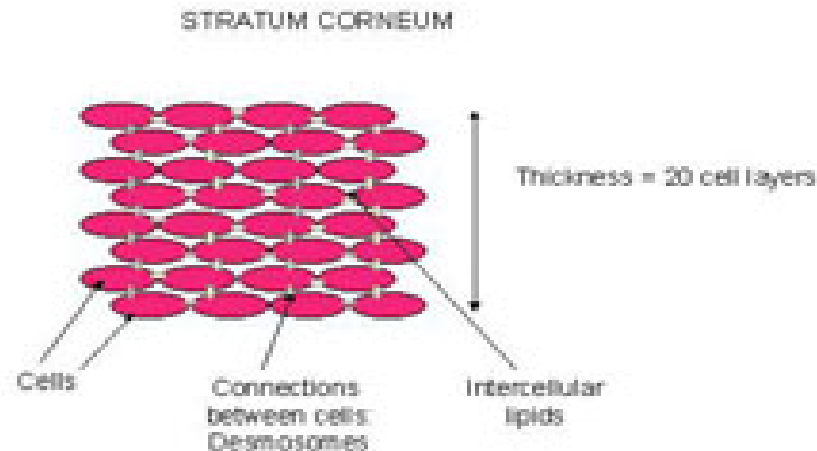
Source: www.pg.com

Stratum Corneum Cohesion

- Desmosomes - main cohesive forces
 - Protein bridges
 - Attach to cell envelopes and lock into position

■ Covalent

■ van der Waals
the corn



rix

l lamellae and

Source: www.netwellness.org



Desquamation

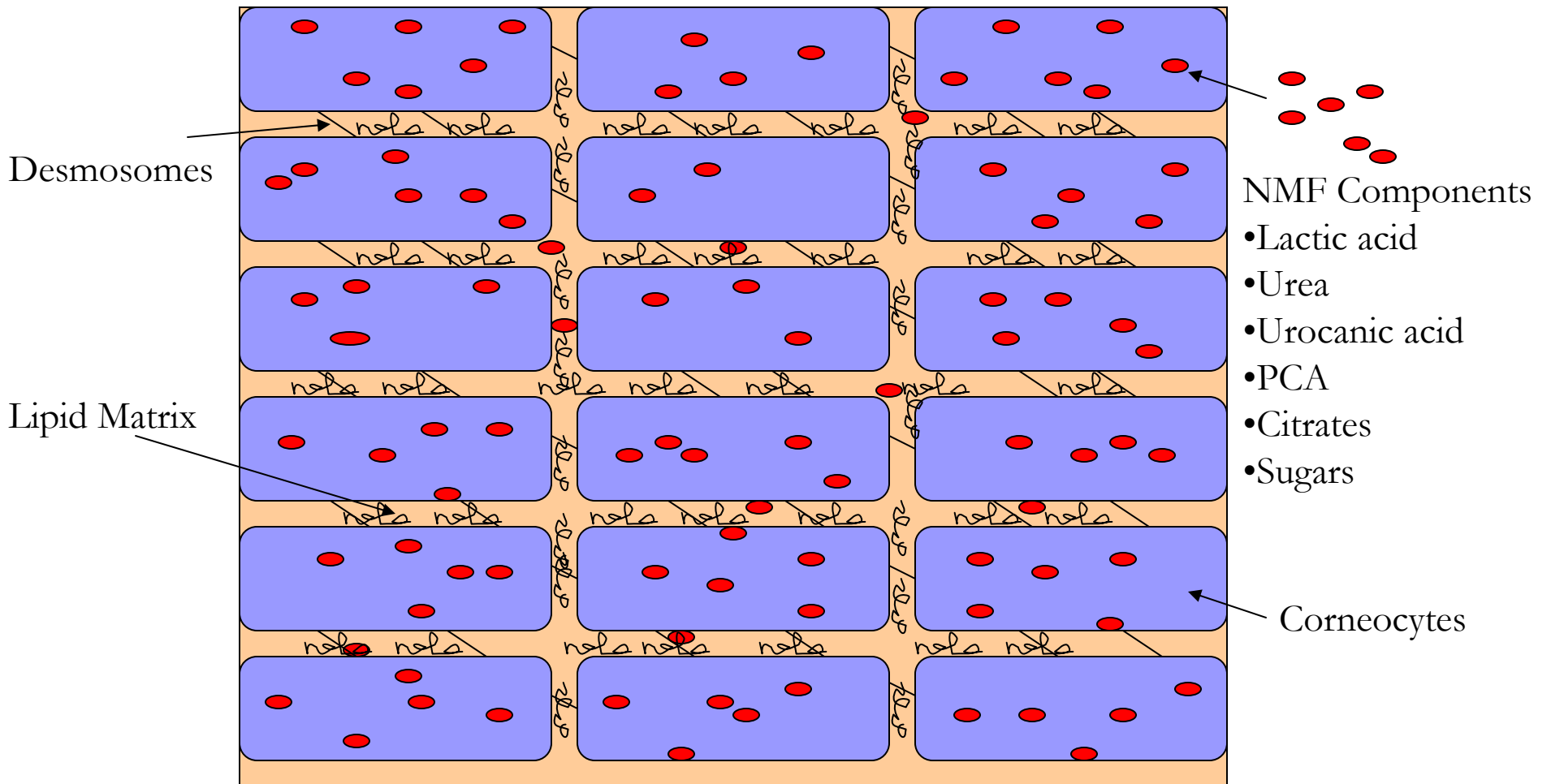
- Corneocytes break apart and are lost
- Enzymatic process – dissolves desmosomes
- These proteolytic enzymes are present in **well-hydrated SC**
- Defective desquamation - corneocytes build up



Natural Moisturizing Factor

- High concentration inside the corneocytes
- Some in the intercellular lipid matrix
- Humectants - absorb water
- Allow for the outermost layers of the SC to remain hydrated

Stratum Corneum



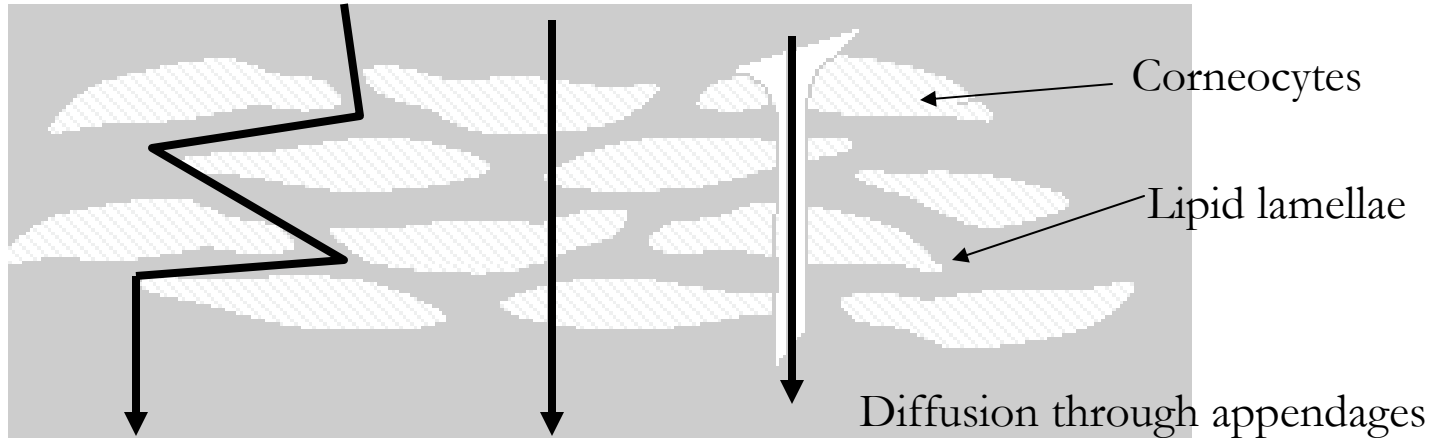


Types of diffusion through skin

- Percutaneous diffusion:
Rate and extent that a chemical is absorbed into and through the skin
- Transepidermal water loss (TEWL)
Passage of water from the body through the skin into the outside environment

Percutaneous Diffusion

SC is rate-limiting step



Intercellular diffusion
through the lipid lamellae
*rate determining
component of the SC
barrier

Transcellular diffusion
through both the
corneocytes
and lipid lamellae

Diffusion through appendages
(hair follicles and sweat ducts)



The Skin Disorder



Xerosis

- Dry skin of a 'normal' or non-pathological state
- Low water content in SC
- Dry and itchy skin
- Occurs when natural moisture is drawn out
- Can be due to cold weather or exposure to too much water

Ichthyosis

What is it?

- A family of disorders in the production and/or desquamation of epidermal cells
- Generically characterized by dry, thickening, scaly skin



Figure 1: Ichthyosis Vulgaris



Figure 2: Ichthyosis Vulgaris

Ichthyosis

Incidence

- Several ichthyoses exist – most affect only one person out of tens of thousands
- Most common forms – Ichthyosis Vulgaris
 - Incidence: 1 in 250

TYPE	INCIDENCE	PER MILLION	YEARLY BIRTHS
Lamellar (recessive)	1 : 200,000	5	19
CIE	1 : 200,000	5	19
EHK	1 : 100,000	10	38
Recessive X-Linked	1 : 6,000	167	635
Darier's Disease	1 : 100,000	10	38
Harlequin Ichthyosis	1 : 200,000	5	19
Ichthyosis Vulgaris	1 : 250	4,000	15,200

Source: www.ichthyosis.com



Ichthyosis Vulgaris

- Reduced water content affects the enzymatic reactions governing desquamation
- Genetic defects – inherited
- Rare cases are acquired – AIDS and cancer
- Currently, there is no cure
- Symptomatic treatment



Treatment



Treatment

- To better treat the disorder, it is necessary to improve skin function by
 - Promoting desquamation
 - Replacing components such as NMF
 - Restoring the lipid barrier
- Current treatments focus on only one step of the cascade of dehydration
- No current product that is offered as a package to treat different causes of poor hydration



Current Treatment

- Many topically applied moisturizers work to trap water
 - occlusives
 - Can be very greasy – unpleasant to consumer
- Some ingredients promote desquamation
 - Keratolytic agents such as lactic acid
- Current treatment has disadvantages
 - Very temporary
 - Focuses on one symptom



Moisturizers

- Maintain hydration and smoothness of the skin
- Putting water back into the skin is no longer the only method for hydrating the skin
- Active ingredients can improve abnormal skin function and structure



Moisturizer Components

■ Active Ingredients

- Occlusives ■ Retard water loss by forming a layer on the surface of skin
- Emollients ■ Fill intercellular spaces with droplets of oil
- Humectants ■ Draw water from the dermis and from air by hydrogen bonding into the epidermis
- Exfoliants ■ Increase sloughing of dead cells on the surface of the skin



Moisturizer Components

■ Complementary Ingredients

- Emulsifying agents ■ Help the emulsion
- Preservatives ■ Prevent microbiologic contamination
- Thickeners ■ Help reach a specific viscosity
- pH Adjustors ■ Adjust the pH of the moisturizer
- Antioxidants ■ Prevent oxidative damage in the skin

Moisturizer Technology

■ Liposomes

- Cheap and simple to manufacture

■ Microemulsions

- Droplets are greater than 0.5 μm in size
- High surface area allow effective transport of active to skin

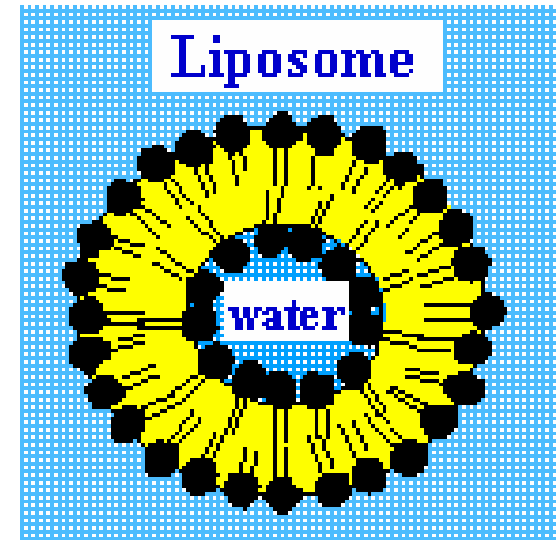
- W/O
- O/W

Advantages

- Low toxicity
- Uptake by endocytosis (can fuse with cell wall)
- Biodegradable and non-toxic in nature
- Replace surfactants and emulsifiers

Disadvantages

- Short circulation half-time



100-200 nm
diameter



Manufacturing Delivery Technology

1. Inverted emulsion with aqueous solution to encapsulate active
2. Emulsified in an organic continuous phase
PEG coating
3. Techniques to control size particle and encapsulation yield (sonication and extrusion)
 - Bath sonicator



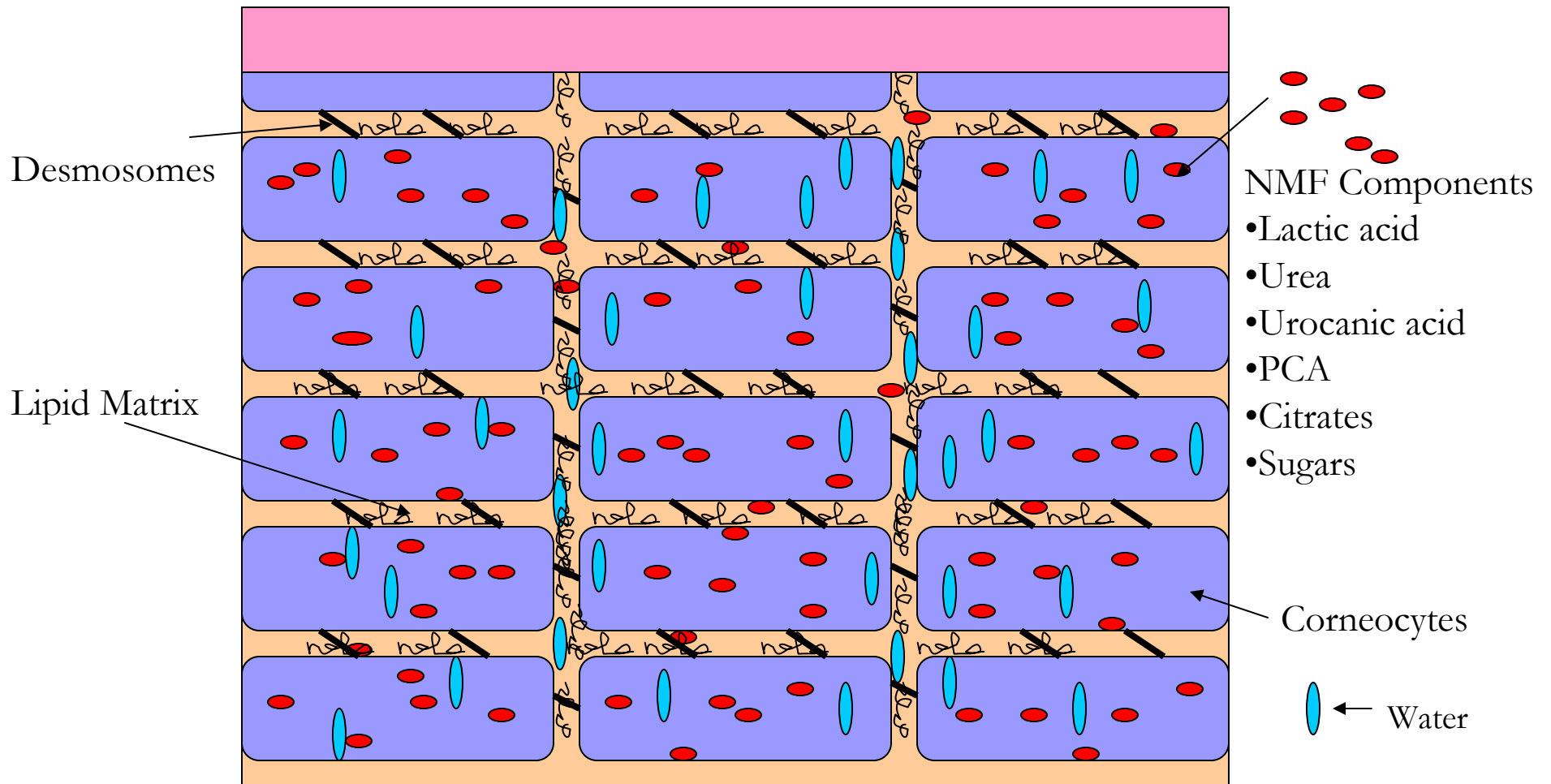
Our Original Product



Skin Rebuilding and Reconditioning Therapy

- Package of 3 separate products:
 1. Pre-Shower Lotion (16 oz)
 - Promotes desquamation
 2. Shower Gel (20 oz)
 - Restores NMF and exfoliates
 3. After-Shower Lotion (16 oz)
 - Rebuilds skin barrier and leaves skin smooth and hydrated

Target of Our Product





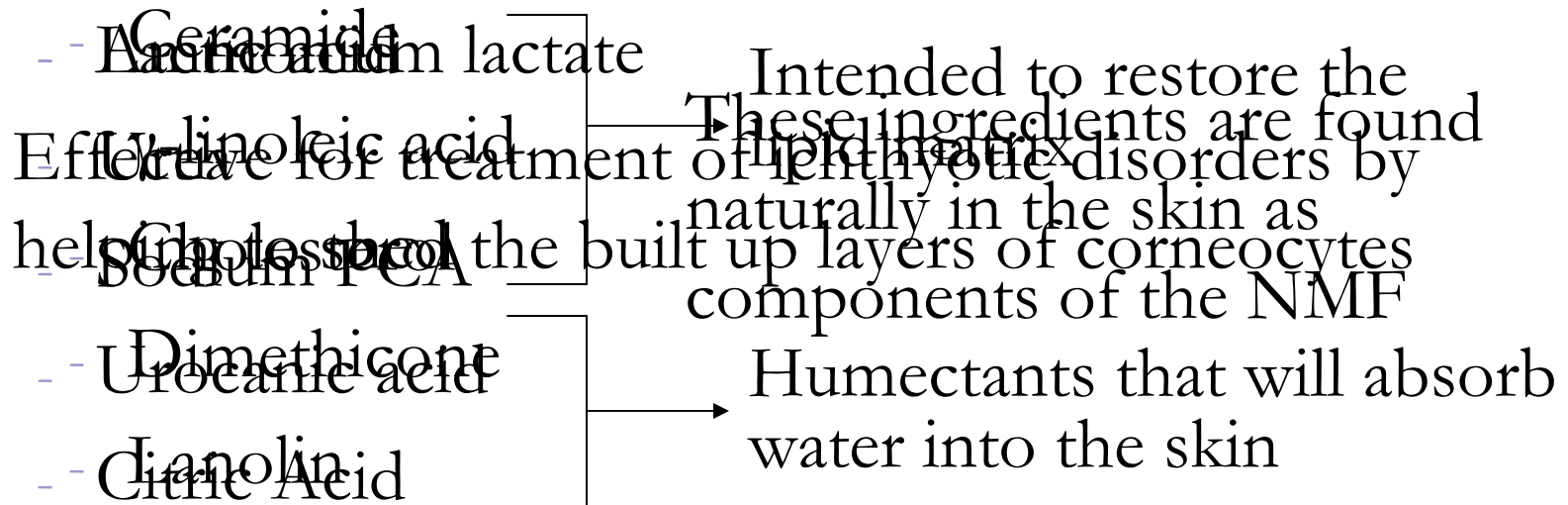
Skin Rebuilding and Reconditioning Therapy

- Our package works as a system of treatment that will surpass current treatments because ours will rebuild skin function producing a longer period of relief
 - Rather than replacing water lost by the SC, our products will give the skin the tools it needs to prevent future dehydration and scaling

Original Formulation

- Active ingredients based on the intended function of each package product

After Shower Lotion






FDA Regulations

- FDA does not regulate cosmetics as it does to drugs

Manufacturers are not obligated to pre-register their
Cosmetics are defined as articles applied to the body in
products before they go into market
any manner ...for cleansing, beautifying, promoting

attractiveness, or altering the appearance
But.....Cosmetic producers must keep ingredients below the
regulated concentration given in the
“Cosmetic Ingredients Review”




Original Formulation: Pre-Shower Lotion

Pre-Shower Lotion Formulation		
Ingredient	Percent (%)	Function
Water	60	Solvent
Ammonium Lactate	10	Desquamation
Retinyl Palmitate	8	Antioxidant
Jojoba Oil	8	Emollient
PEG-4	8	Emollient/Liposome Formation
Cetyl Alcohol	2.9	Emulsifier
Octyldodecanol	2.9	Thickener
Phenoxyethanol	0.196	Preservative
Maleic Acid	0.004	pH Adjuster



Original Formulation: Shower Gel

Shower Gel Formulation		
Ingredient	Percent %	Function
Water	52	Solvent
Polysorbate-20	20	Surfactant
Cocoamidopropyl Betaine	5	Surfactant
Lactic Acid	4	Exfollient/NMF
Urea	4	NMF
Sodium PCA	3	NMF
Urocanic Acid	3	NMF
Citric Acid	3	NMF
Oleic Acid	3	Emollient/Thickener
Cetyl Alcohol	2.796	Emulsifier
Phenolxyethanol	0.2	Preservative
Maleic Acid	0.004	pH Adjustor



Original Formulation: After-Shower Lotion

After-Shower Lotion Formulation		
Ingredient	Percent %	Function
Water	60	Solvent
Dimethicone	10	Humectant
Lanolin	8	Humectant
PEG-4	6.996	Emollient/Liposome Formation
Cetyl Alcohol	5	Emulsifier
Ceramide	3	SC Lipid/Humectant
Isostearic Acid	2.8	Thickener
Palm Oil	2	Emollient
γ-Linoleic Acid	1	SC Lipid
Cholesterol	1	SC Lipid
Phenoxyethanol	0.2	Preservative
Maleic Acid	0.004	pH Adjustor



Cost for the Package

	Cost (million \$)
Raw Material Cost/yr	51.62
Total Product Cost/yr	58
Annual Product Revenue/yr	16.2
NPW	-125.54



Substitutes and Modeling Consumer Attitudes



Substitute Ingredients

- Ingredients costing more than \$10⁵ / year were considered for replacement with less expensive chemicals serving the same purpose
- Active ingredients were not substituted
- PEG was also not substituted - liposome formation

Pre-Shower Lotion Substitutes

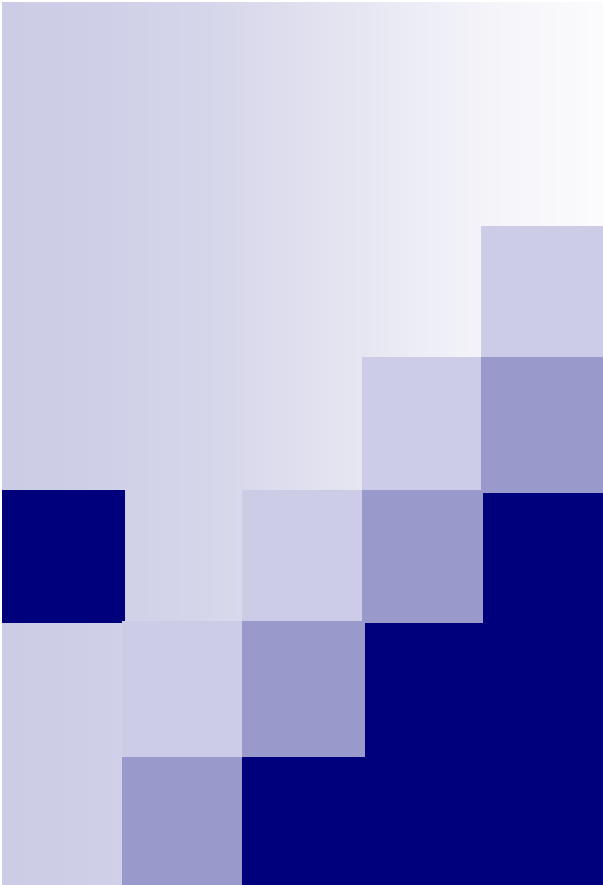
Material	Function	Substitutes
Deionized Water	Solvent	-----
Ammonium Lactate*	Desquamation	-----
Jojoba Oil	Emollient	Castor Oil
PEG	Emulsifier/Liposome Formation	-----
Octyldodecanol	Thickener	Paraffin Oil
Retinyl Palmitate (Vitamin A Palmitate)	Antioxidant	Ascorbic Acid
Cetyl Alcohol	Emulsifier	Polysorbate 20
Phenoxyethanol	Preservative	-----
Maleic Acid	pH Adjuster	-----
	Fragrance	Peppermint Oil

Shower Gel Substitutes

Material	Function	Substitutes
Deionized Water	Solvent	-----
Polysorbate-20	Surfactant	-----
Cocoamidopropyl Betaine	Surfactant	-----
Lactic Acid	NMF	-----
Urea	NMF	-----
Sodium PCA	NMF	-----
Urocanic Acid	NMF	-----
Citric Acid	NMF	-----
Oleic Acid	Emollient/Thickener	-----
Cetyl Alcohol	Emulsifier	Polysorbate 20
Phenoxyethanol	Preservative	-----
Maleic Acid	pH Adjuster	-----
	Fragrance	Peppermint Oil

After-Shower Lotion

Material	Function	Substitutes
Deionized Water	Solvent	-----
Dimethicone	Humectant	Sorbitol
Lanolin	Humectant/Emollient	Isopropyl Palmitate
PEG	Emollient/Liposome Formation	-----
Cetyl Alcohol	Emulsifier	Polysorbate 20
Isostearic Acid	Thickener	-----
Palm Oil	Thickener	Paraffin Oil
Ceramide	SC Lipid/Emollient	-----
γ-linoleic acid	SC Lipid	-----
Cholesterol	SC Lipid	-----
Phenoxyethanol	Preservative	-----
Maleic Acid	pH Adjustor	-----
	Fragrance	Peppermint Oil



Consumer Preferences Based on Physical Properties

Happiness Model

- Optimizes relative happiness by determining formulation based on 4 factors:

1. Creaminess

Based on surface tension of active ingredients and PEG

$$Creaminess = \frac{P}{\mu} \left(\frac{Smoothness * Thickness}{4} \right)^{0.5}$$

These coefficients are weighted based on functions

$$Smoothness = \left(\frac{C_{friction}}{1000} \right)^{0.5}$$

Gelling ability determined from:
 [1] determined from viscosity experiment and
 general recommendations

$$\frac{\left(\frac{C_{DM}}{C_w^0} \right)^{DM} * \left(C_w^0 \right)^{HM}}{C_w^{Ideal}}$$

Q_G neglected at low pressure

Diffusion Model

$$\frac{\left(\frac{C_w}{C_w^0}\right)_{DM} * (C_w^0)_{HM}}{C_w^{Ideal}}$$

- Accounts for mass transport through:
 - Oil Phase
 - Water Phase
 - Protein Phase

- Disregards:
 - Diffusion through the appendages since it accounts for 0.1% of the total surface area of the skin
 - TEWL since it is constant and represents a very small portion of the water contained by the body

Diffusion Model of the SC

- This equation was derived using a diffusion model based on Fick's Law


$$\frac{C_w}{C_w^o} = 1 - \frac{x}{L_{sc}} - \frac{2}{\pi} \sum_{n=1}^{\infty} \frac{1}{n} \sin \frac{n\pi x}{L_{sc}} e^{-\frac{D_{sc} n^2 \pi^2 t}{R_{sc} L_{sc}^2}}$$

This model is a function of time and location in the skin

- 10 minutes- Pre-shower Lotion
- 5 μm - Pre-shower Lotion
- 3 minutes- Shower Gel
- 15 μm - Shower Gel
- 12 minutes- Post-Shower Lotion
- 15 μm - After-Shower



Demand Model



Market Trends

- Patients will always need a product to treat the disorder
 - No cure
- Demand should never decrease
 - No cure
 - Approximate constant number of people affected by the disorder

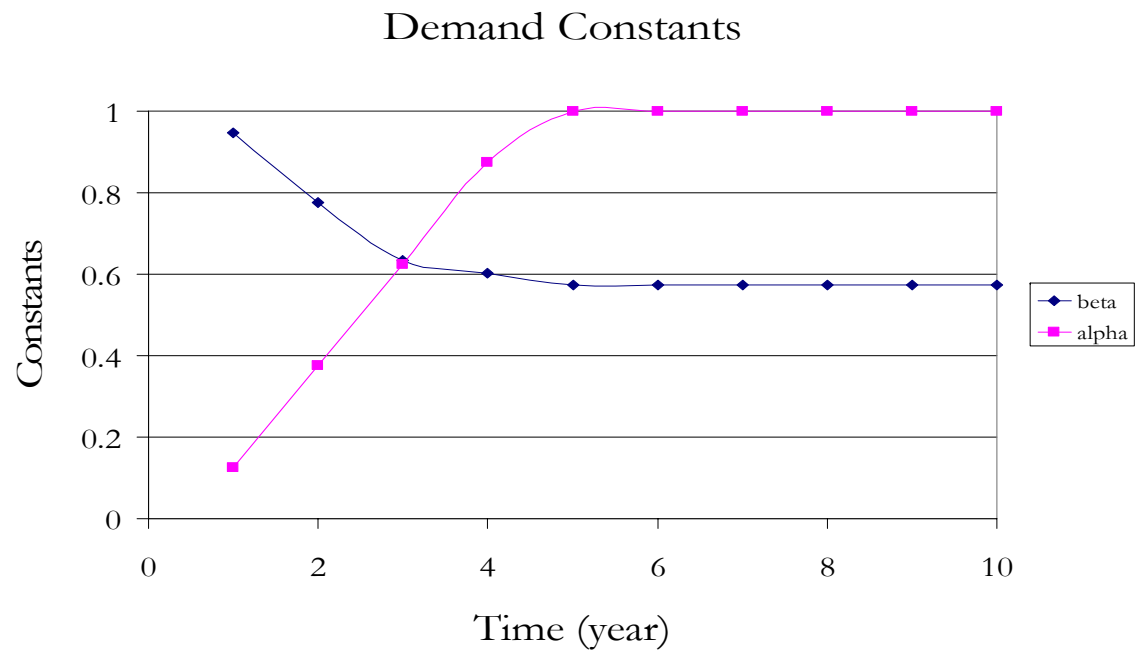
Demand Model

$$\beta p_1 d_1 = \alpha p_2 d_2$$

$$\beta = \frac{H_2}{H_1}$$

$$d_1 = D - d_2$$

$$d_1 = \frac{\alpha D p_2}{\alpha p_2 + \beta p_1}$$





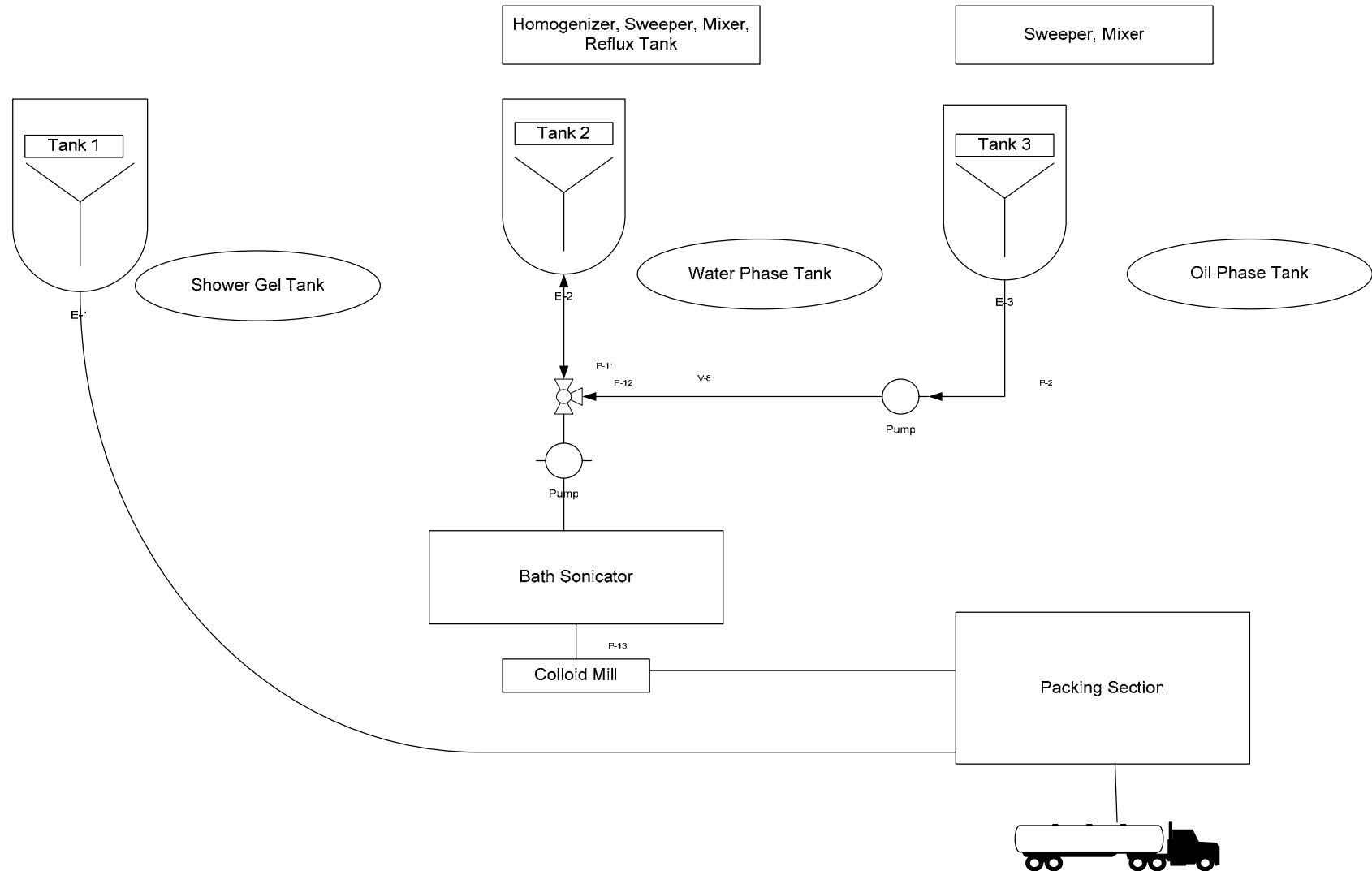
Distribution and Advertising

- Promoting our package to the Ichthyosis community by:
 - Free samples to:
 - General practitioners and dermatologists
 - Patients registered on Ichthyosis registries
 - Advertisements in:
 - Ichthyosis organization websites
 - Posting in medical offices



Manufacturing

Process Design





Equipment

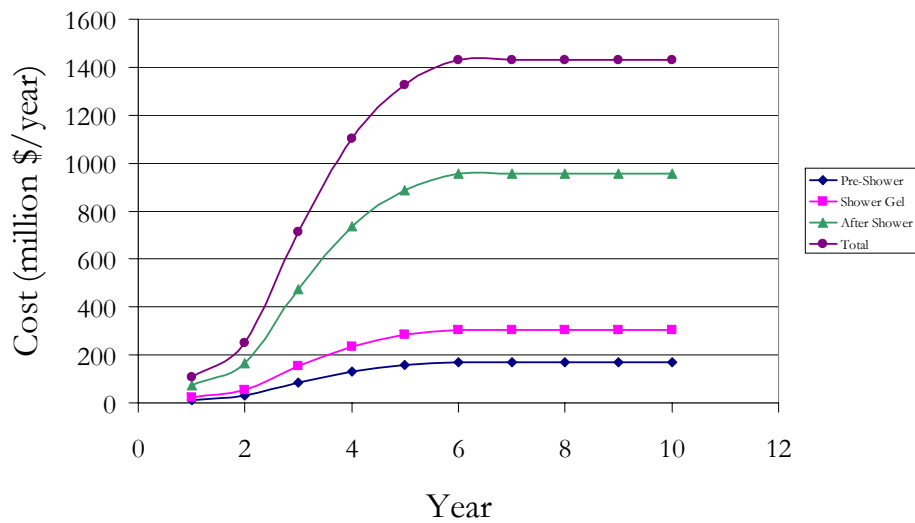
Equipment	Specifications	Cost (\$)
Tank 1: Shower Gel	15.1 m ³	43,750
Tank 2: Lotion	12.1 m ³	38,700
Tank 3: Lotion	12.1 m ³	38,700
Colloid Mill	7.5 hp	15,000
Bath Sonicator	115 V	800
Homogenizer	100 L/hr	11,500
2 Pumps	0.0145 m ³ /s	5,500
Total Equipment Cost		\$154,000



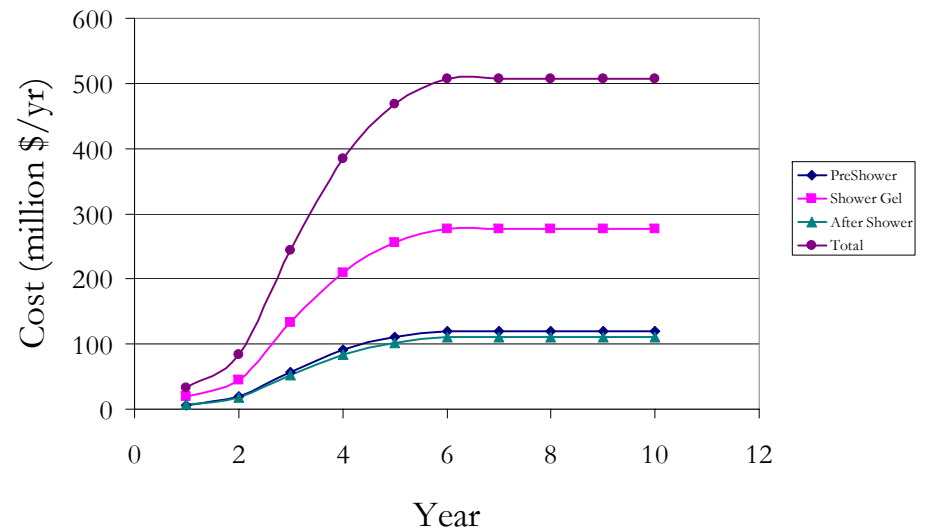
Economic Analysis

Raw Material Cost

Original Raw Material Cost



Substitute Raw Material Cost





Economic Evaluation

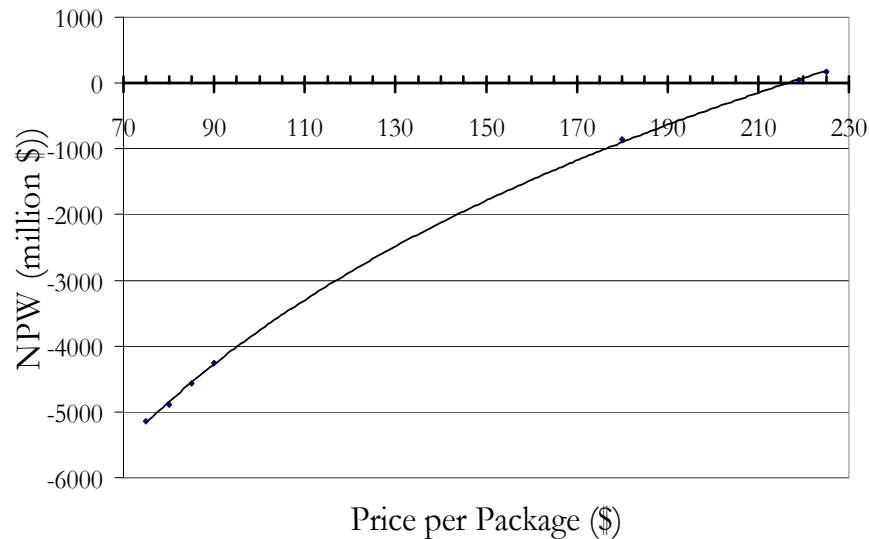
Optimized Original Formulation Optimized Substitute Formulation

Equipment Cost	0.153186
Fixed Capital Investment	0.849263
Total Capital Investment	0.999233
Net Profit	-6986.15
NPW	-4250.14

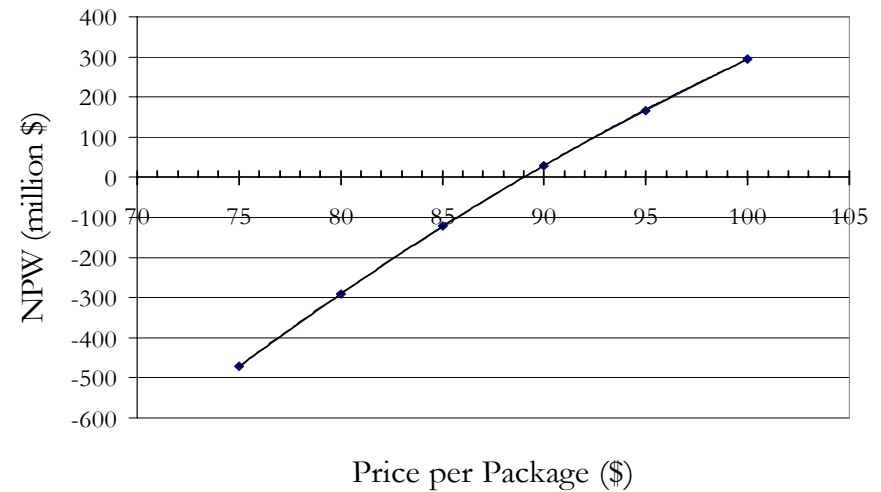
Equipment Cost	0.153186
Fixed Capital Investment	0.849263
Total Capital Investment	0.999233
Net Profit	30.98
NPW	28.55

Net Present Worth vs Package Price

Optimal Formulation NPW vs Package Price



Substitutes NPW vs Package Price



Final Formulation

Pre-Shower		Shower Gel		After-Shower	
Ingredient	%	Ingredient	%	Ingredient	%
Deionized Water	55	Deionized Water	50.7089	Deionized Water	50
Ammonium Lactate	10	Sodium PCA	3	Isopropyl palmitate	2
Ascorbic Acid	2.386	Lactic Acid	1	Sorbitol	2
Castor Oil	5.006	Urocanic Acid	1.5	Ceramide	0.003
Polysorbate 20	9.816	Citric Acid	2.73727	γ -linoleic acid	0.001
Paraffin Oil	3.015	Urea	9	Cholesterol	0.001
Maleic acid	0.004	Polysorbate-20	20	Polysorbate 20	15.99
Phenoxyethanol	0.221	Cocoamidopropyl Betaine	5	Paraffin Oil	10
PEG	14.551	Oleic Acid	6	Isostearic Acid	5
Peppermint Oil	0.001	Phenoxyethanol	1	Maleic acid	0.004
		Maleic acid	0.00393	PEG	15
		Peppermint Oil	0.04994	Peppermint Oil	0.001
				Phenoxyethanol	0.001



Questions?