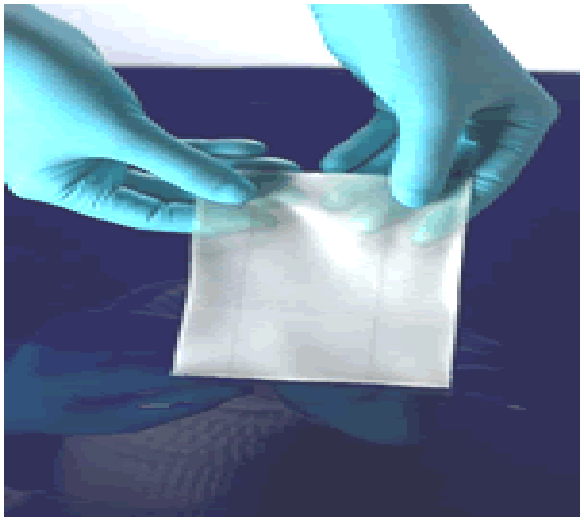
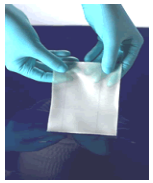
REPLIDERM Inc.

GROUP 8

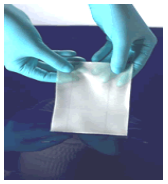
Tiwalade Ashaye,
Joseph Azzarello,
Ben Fairbanks,
Mitch Hargis,
Krupa Patel,
Holap Tang



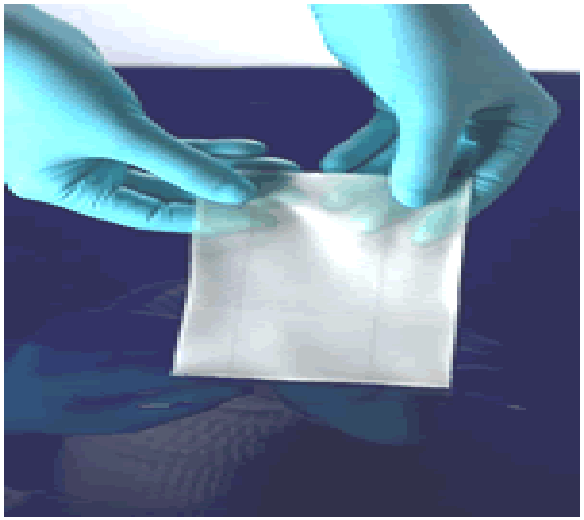


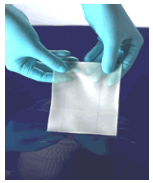
OVERVIEW

- Background/Review of current conditions
- Objective of RepliDerm
- Production plan
- FDA Approval Process
- Business/Market Plan



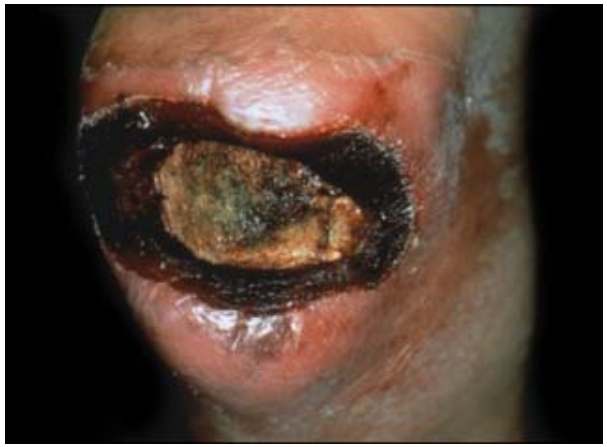
BACKGROUND

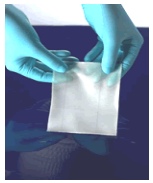




Problem

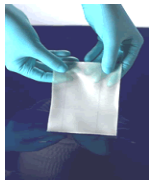
- 270,000 burn victims per year in the U.S. requiring hospitalization
- 1.5 million diabetic patients in the U.S. with wound ulcers
- Various narcotizing infections (flesh eating infections)





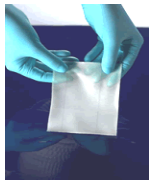
Treatments Available

- Split thickness autograft
- Donor allograft
- Synthetic allograft
- Synthetic allograft with seeded neo-natal fibroblasts
- Temporary covering from biological donor

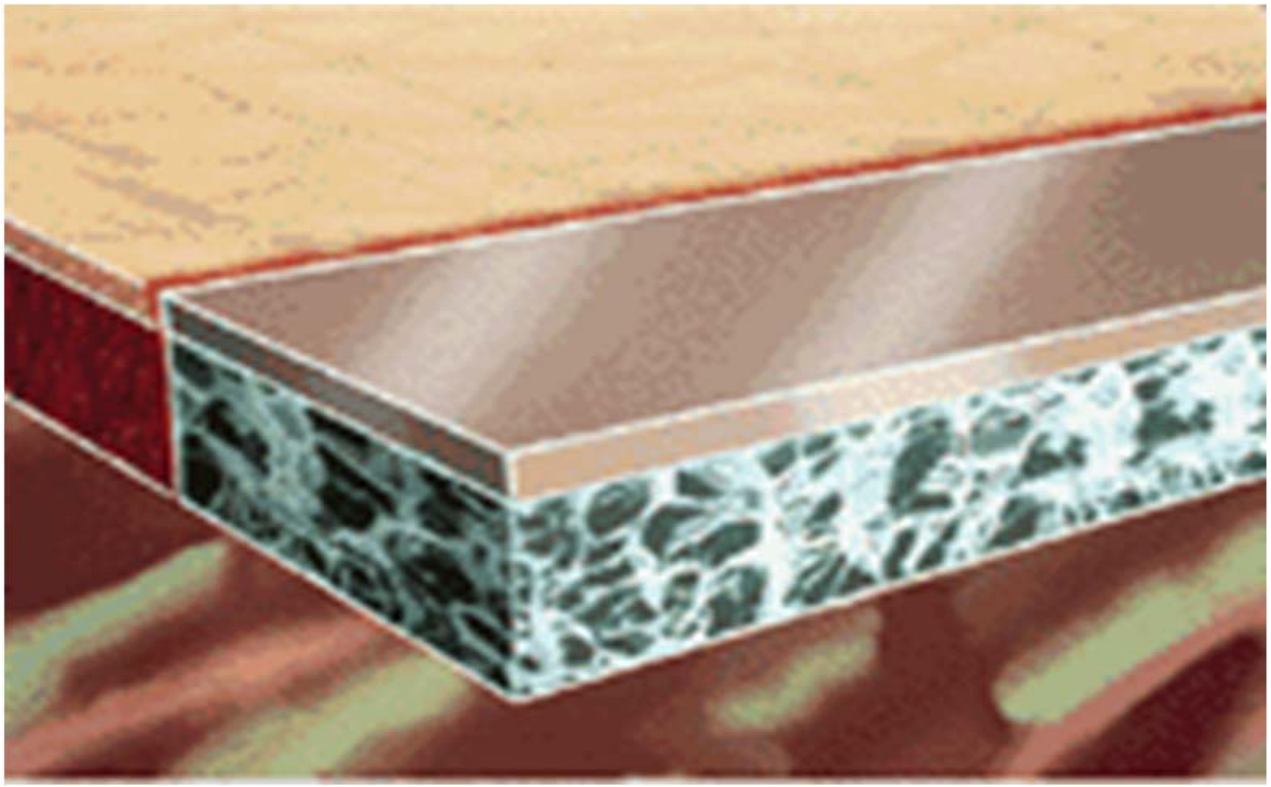


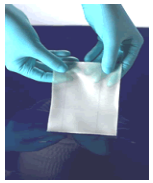
Advantages of Existing Treatments

Procedure (Product)	Advantages	Disadvantages	Price/in^2
Split Thickness Autograft (Surgical treatment)	Inexpensive No rejection	Extensive scarring Limited donor sites	$0
Donor Allograft (AlloDerm)	Relatively Inexpensive	Disease transmission 10% Rejection Small wounds only	$7/in^2
Synthetic Allograft with Seeded Cells (Epicel)	No epidermal graft needed 5% Rejection	Fragile	$102/in^2
Synthetic (Integra)	Strong & supple Protective layer 5% Rejection	Epidermal autograft required	$42/in^2

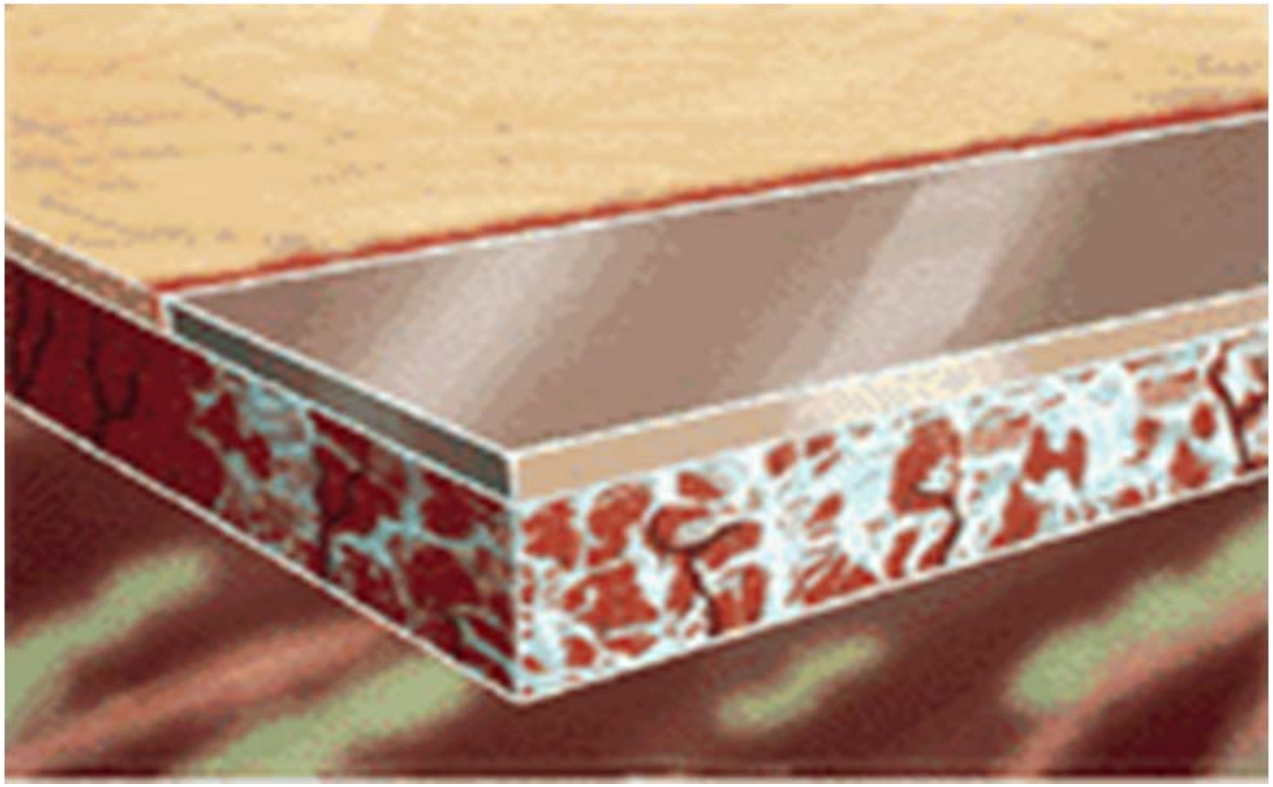


On the Market: Integra Dermal Regeneration Template

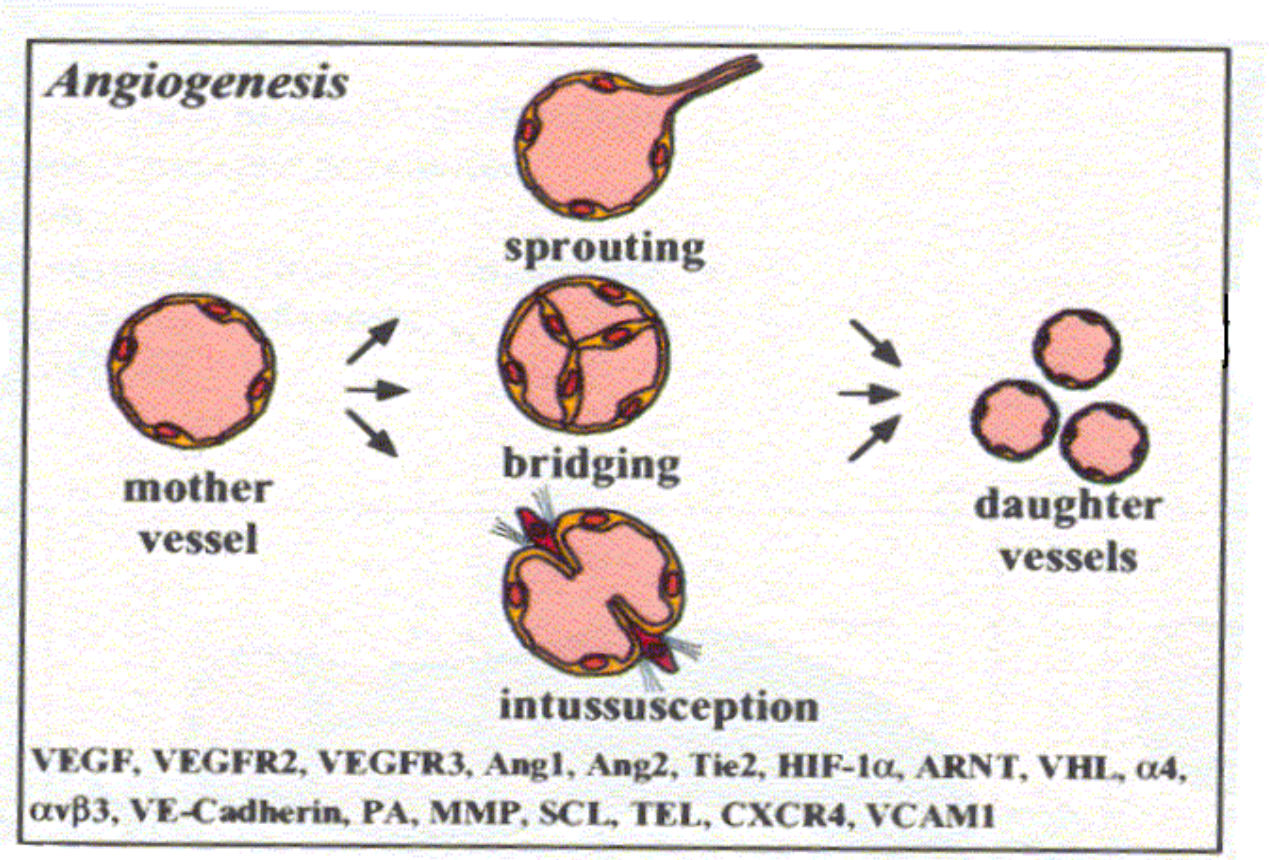


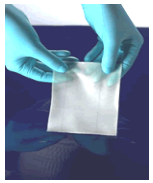


On the Market: Integra Dermal Regeneration Template

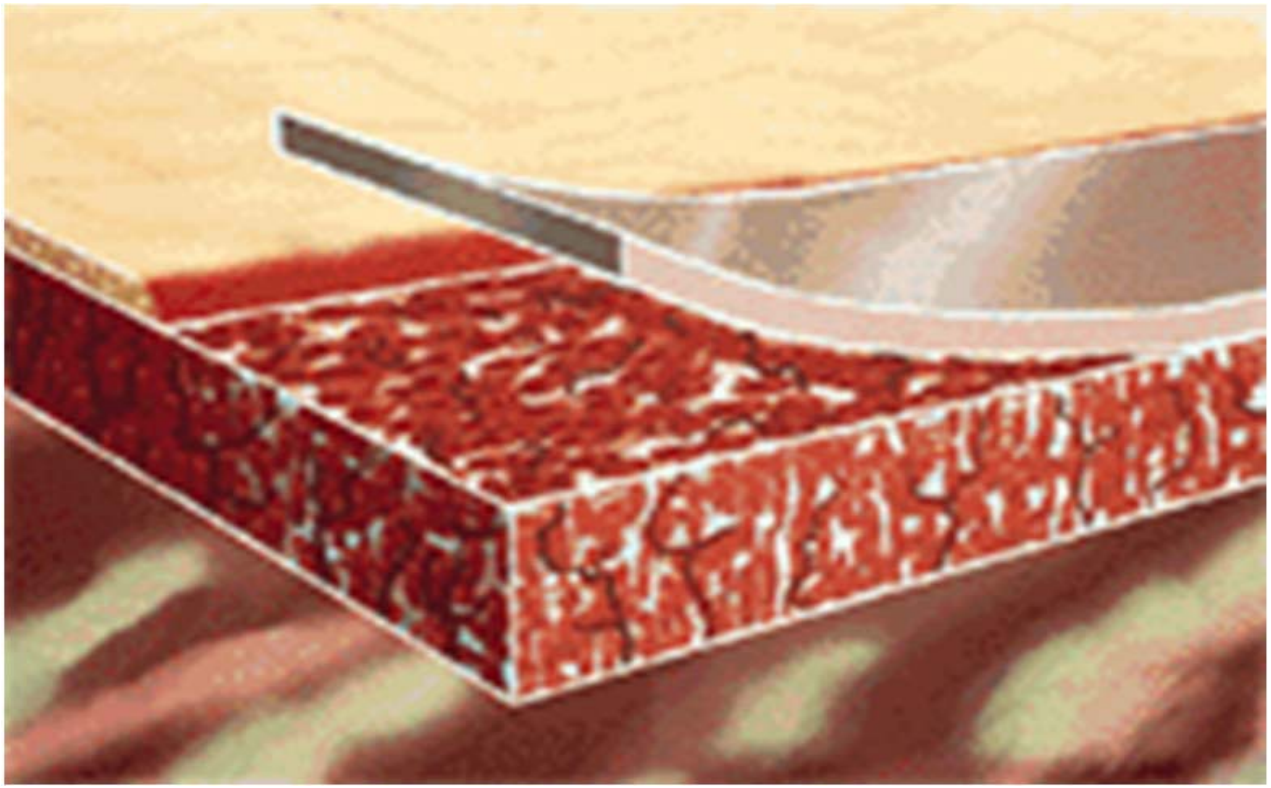


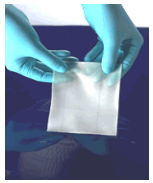
Mechanism for Angiogenesis



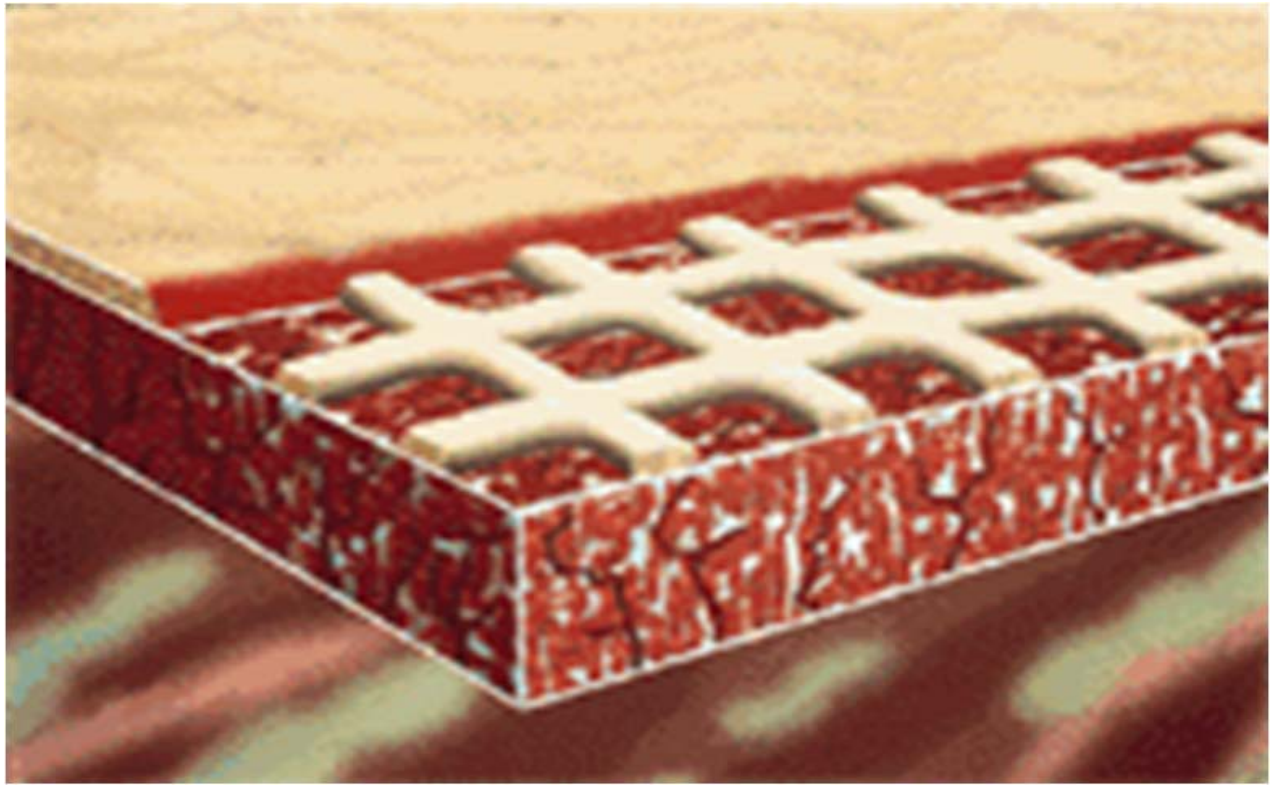


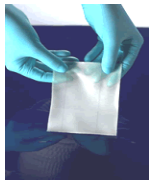
On the Market: Integra Dermal Regeneration Template



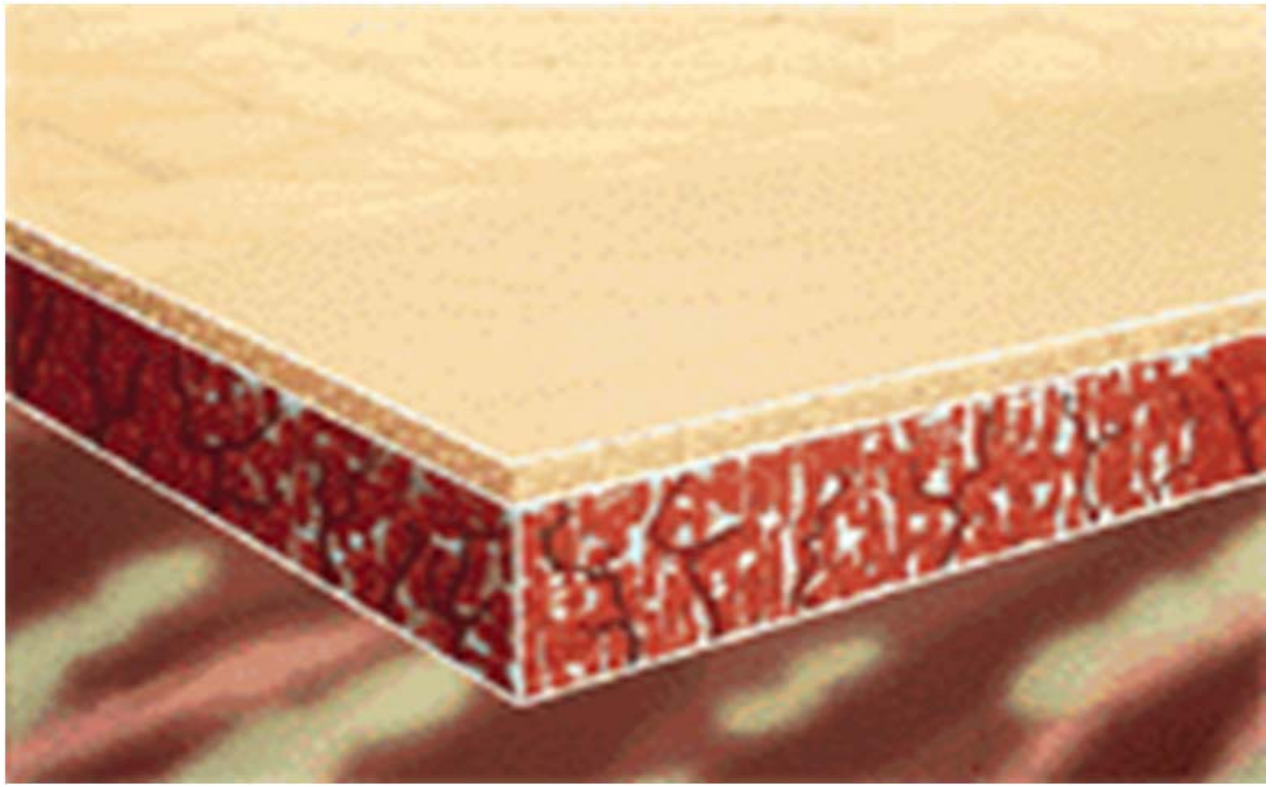


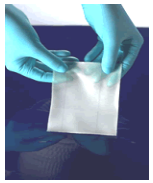
On the Market: Integra Dermal Regeneration Template





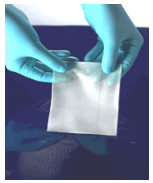
On the Market: Integra Dermal Regeneration Template





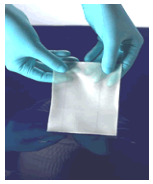
Product Objective

- To produce a synthetic dermal replacement template that increases the speed of vascularization and quality of burn and wound treatment.

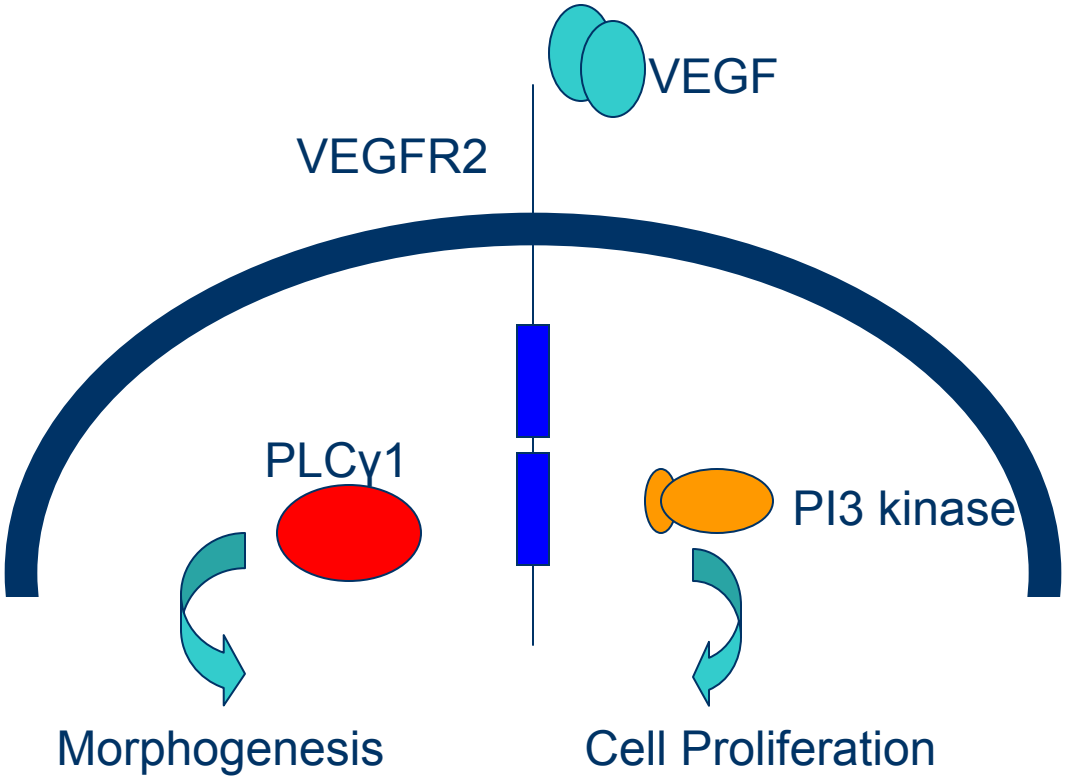


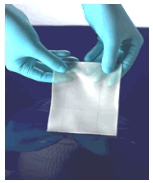
Growth Factors

- Basic Fibroblast Growth Factor-BFGF
- Acidic Fibroblast Growth Factor-AFGF
- Platelets Derived Growth Factor-PDGF
- Vascular Endothelial Growth Factor-VEGF



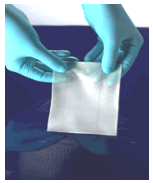
VEGF Stimulation of Angiogenesis





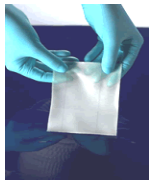
Methods of Delivery

- Daily Injections
- VEGF in the crosslinked collagen matrix
- VEGF in suspension in pores of matrix
- Controlled release microparticles



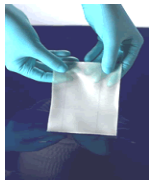
Controlled Release particles

- Optimize rate of vascularization by altering:
  - Number/VEGF Concentration of Microcapsules
  - Location of Microcapsules
  - Size of Microcapsules

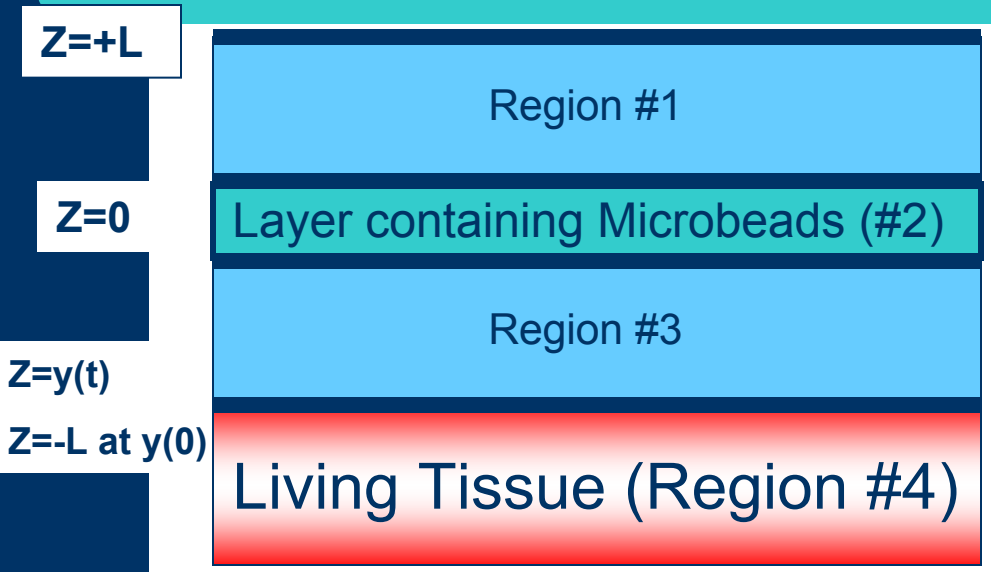


Microcapsule Diffusion Model

- A model of the VEGF's motion through the implant could be created and used to create a more-effective product
- If a model with predictive capabilities was created, then the ideal initial concentration and placement of the microbeads could be determined

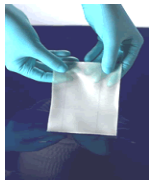


Microcapsule Diffusion Model



Microbead region releases VEGF with rate r* and at a concentration c*

- No flux across top layer: ($\delta c/\delta z = 0$ @ z=L)
- Bottom layer rises with time as tissue vascularizes into graft
- Living tissue carries away VEGF with a rate $k_v f(c_3)$
- Regions 1,2, and 3 have a diffusion coefficient D_1
- Region #4 has diffusion coefficient D_2
- Molar fluxes are equal at region interfaces

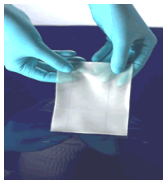


Microcapsule Diffusion Model

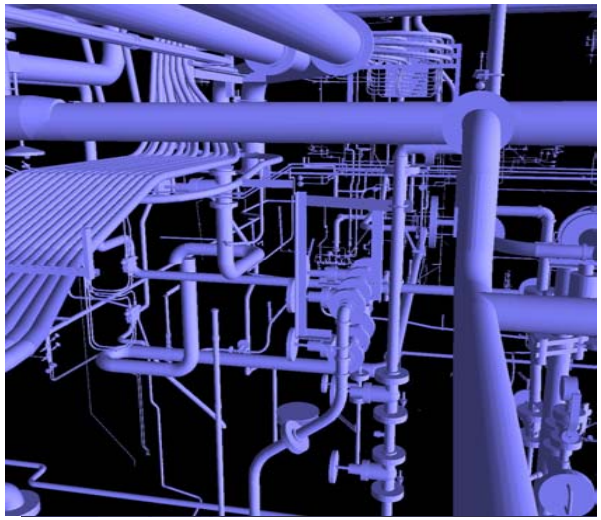
- With the model described in the previous slide, the following expression is obtained:

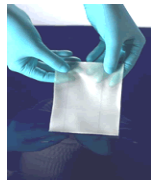
$$\frac{dy}{dt} = \frac{k_g r^*}{k} e^{-y^2 / \alpha_3 \sqrt{t}}$$

- y(t) (the “rate of healing”) can be approximated from the above model

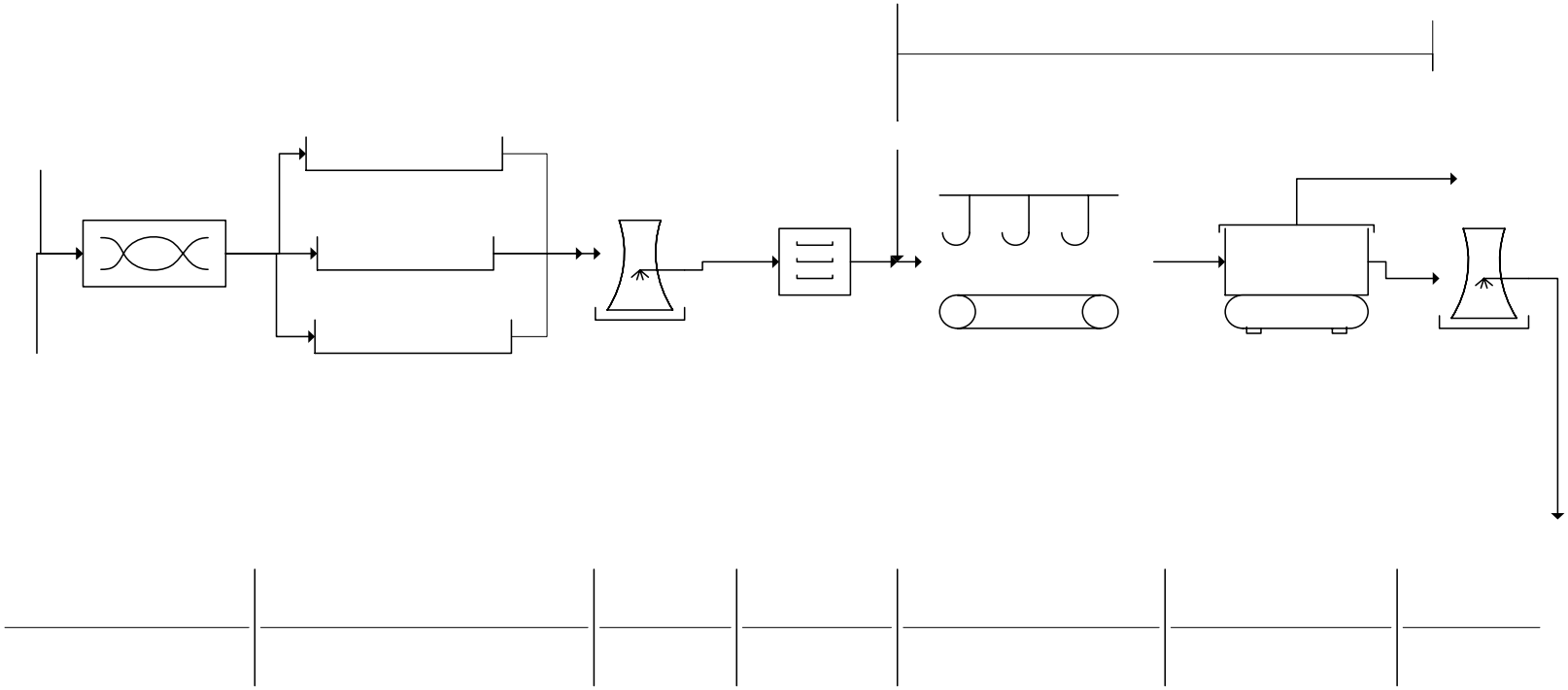


PRODUCTION PROCESS

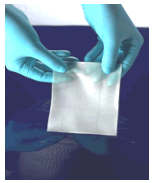




REPLIDERM PRODUCTION PROCESS

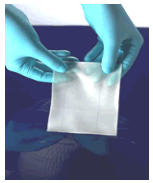


Add Bovine
Tendeon
Collagen
Dispersion



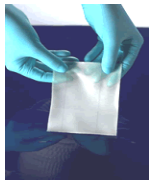
REPLIDERM PRODUCTION

- Raw material needed
- Equipments needed
- Description of process
- Human labor needed
- Facility layout



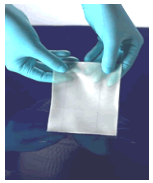
REPLIDERM Production

- Raw materials needed
- Equipments needed
- Description of process
- Human labor needed
- Facility layout



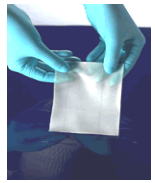
REPLIDERM Production (Raw materials)

Procedure (Product)	Description	Use
Bovine Collagen	Extracellular protein	Support and structure of matirx
Chondroitin 6-Sulfate	Glycoproteins known as proteoglycans found in shark cartilage	forms the ground substance in the extracellular matrix of connective tissue.
Silastic	Silicon layer	Used as a temporary barrier to protect against infection
PLGA(polylactic glycolic acid	Biodegradable, biocompatible polyester	Manufacture of microspheres
PEG (**Polyethylene-glycol**)	Polymer	Speeds up degradation of the microbeads. It also forms the sphere shape of the beads
VEGF	As described earlier	A protein growth factor



REPLIDERM Production

- Raw material needed
- **Equipments needed**
- Description of Process
- Human labor needed
- Facility layout



Repliderm Production (Equipments Needed)

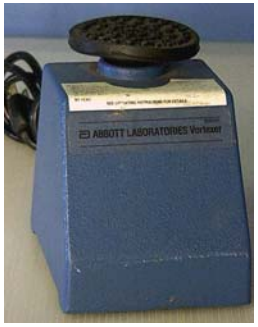
Blender

Tissue Homogenizer

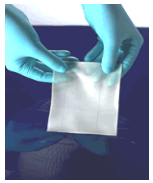
- Small Equipment
- Batch processes

Centrifuge

Vacuum oven

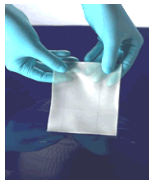


Vortex

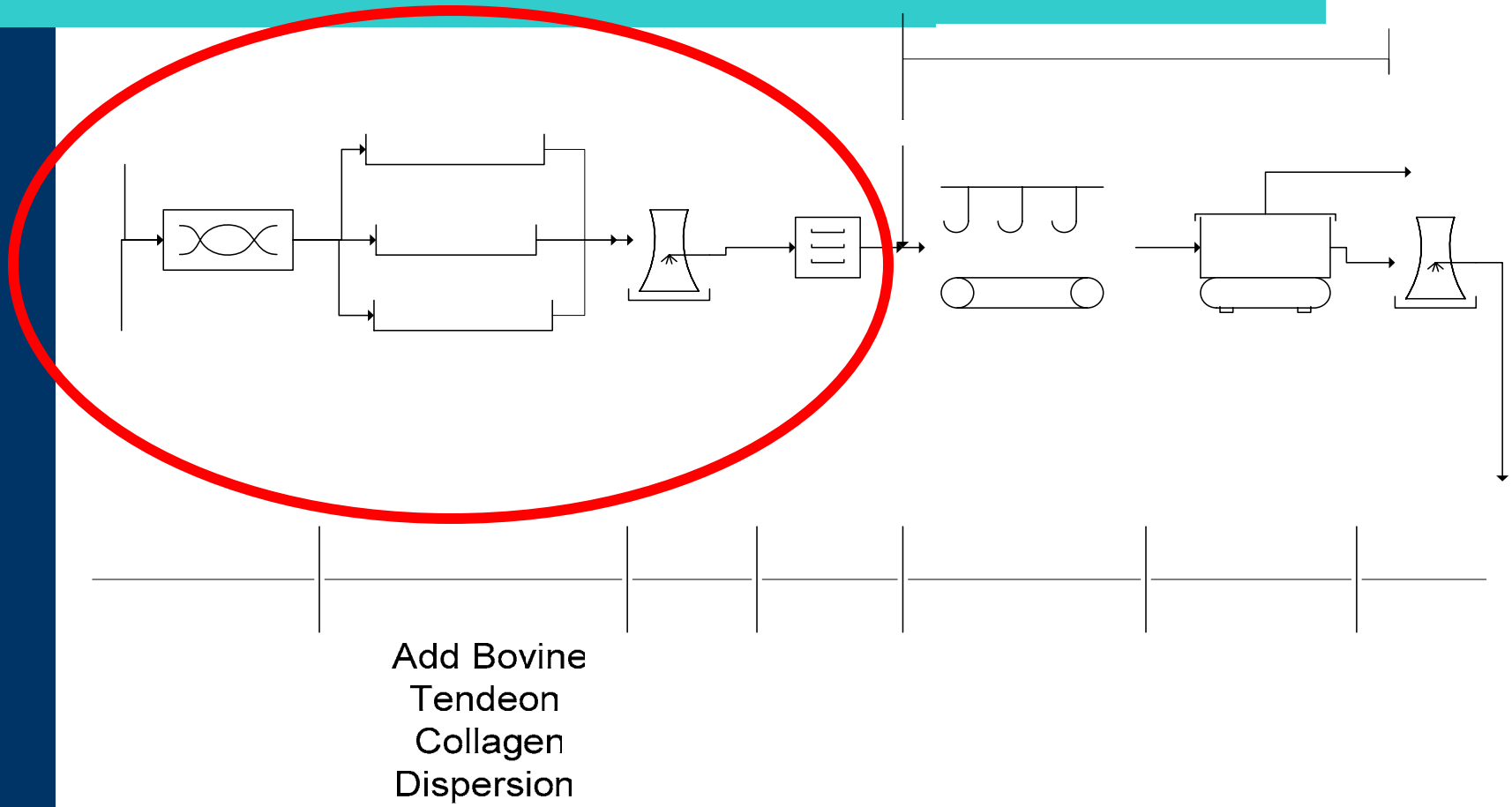


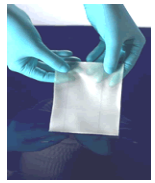
REPLIDERM Production

- Raw material needed
- Equipments needed
- **Description of Process**
- Human labor needed
- Facility layout

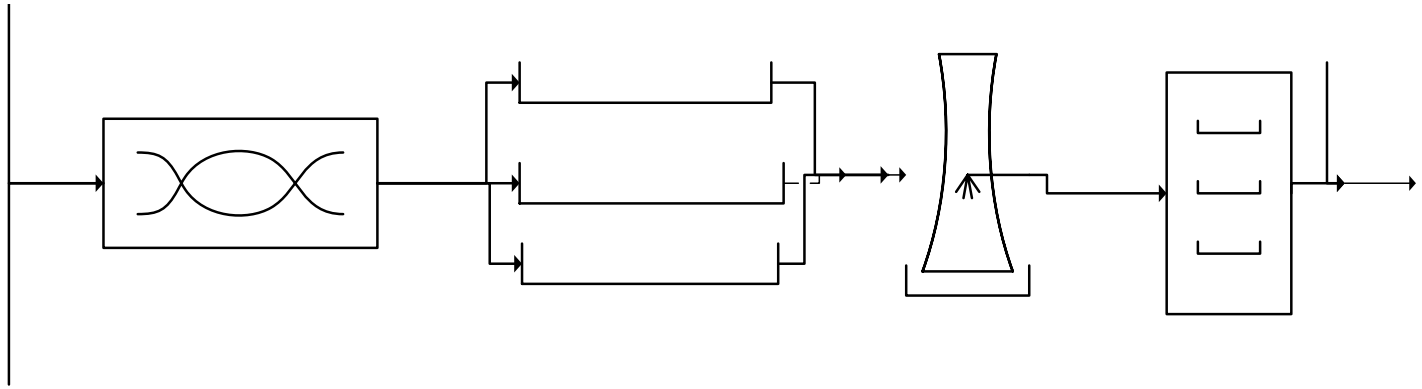


REPLIDERM PRODUCTION PROCESS

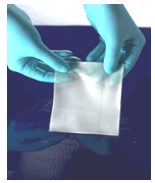




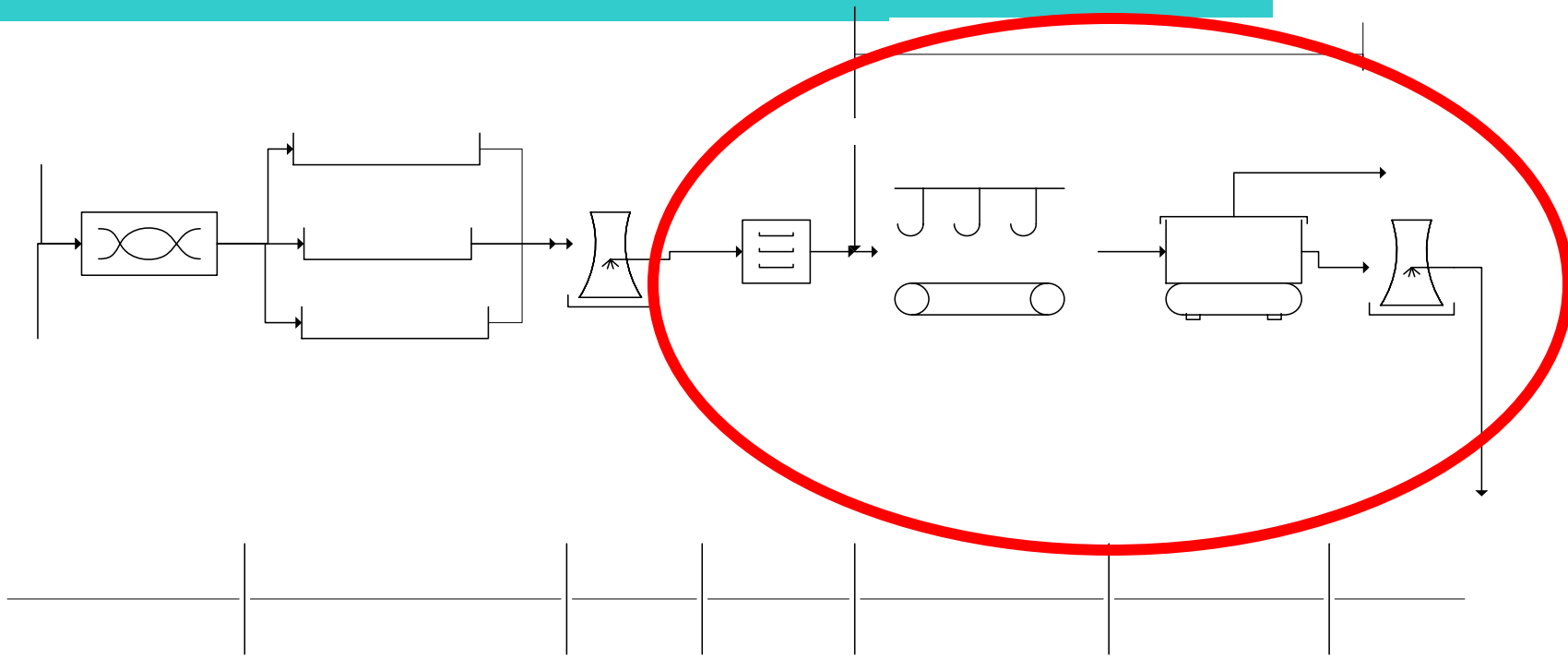
Before Microbead addition…



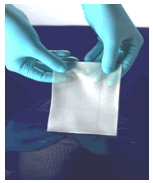
Add Bovine
Tendeon
Collagen



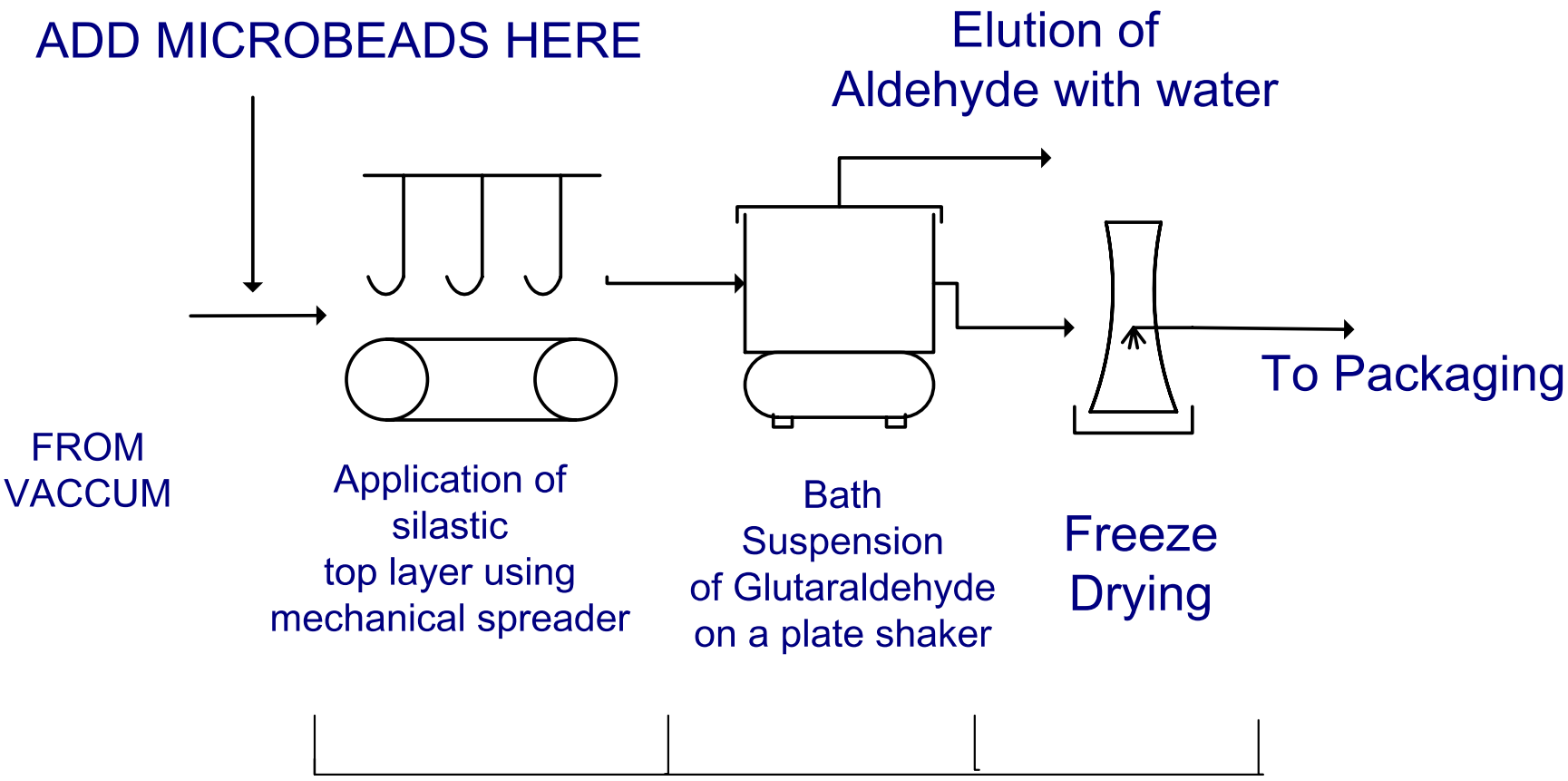
REPLIDERM PRODUCTION PROCESS

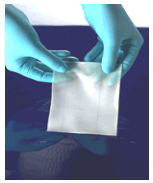


Add Bovine
Tendeon
Collagen
Dispersion



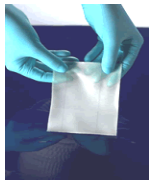
After Microbead addition…



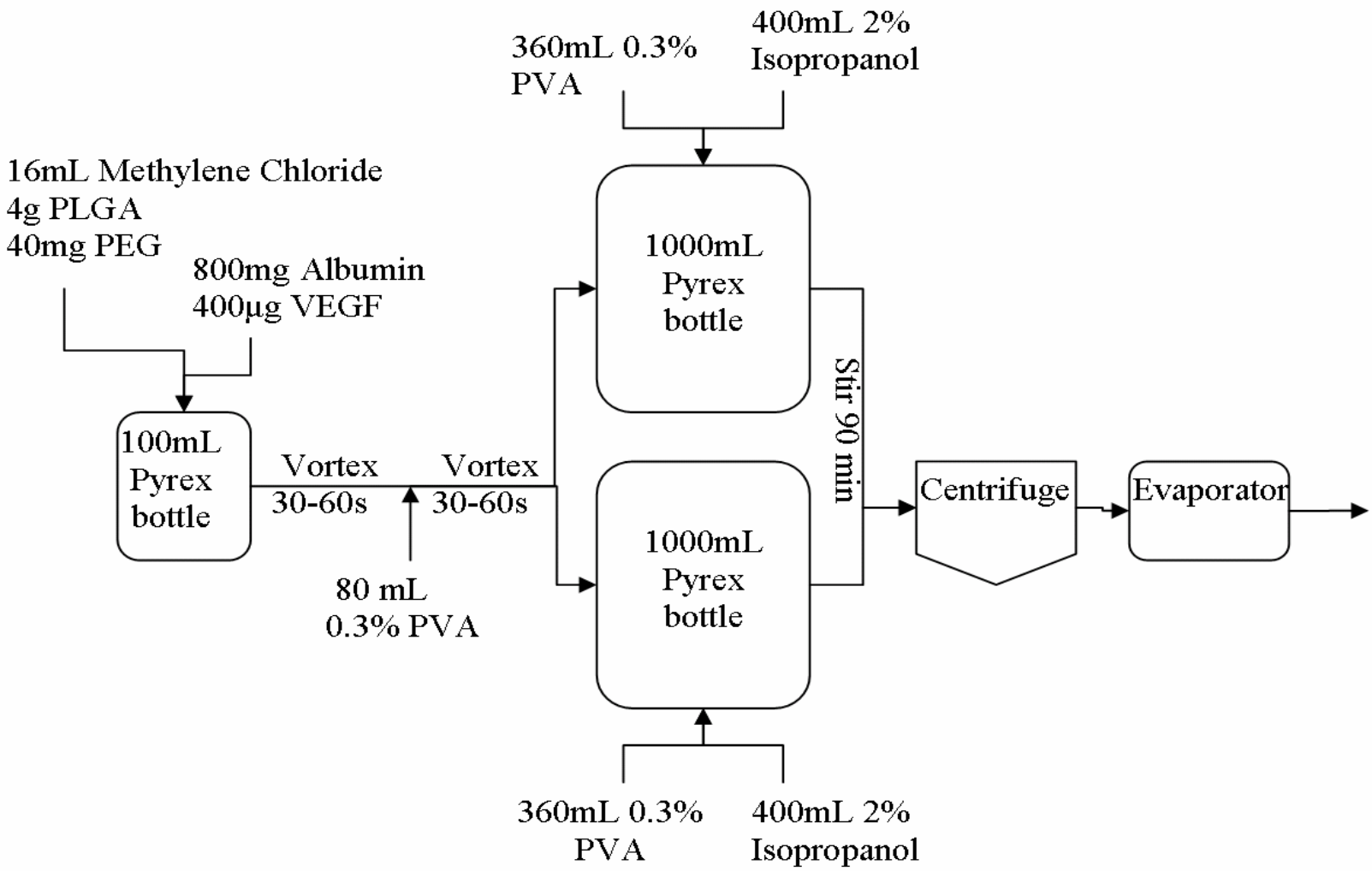


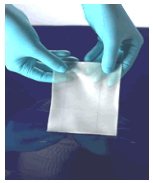
Microcapsule Production

- Raw materials -
  - PLGA Poly(lactic-co-glycolic) acid (50:50)
  - PEG (Polyethylene- glycol)
  - VEGF (Vascular endothelial growth factor)
  - Albumin
  - PVA (polyvinyl alcohol)
  - Isopropanol



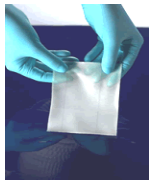
MICROCAPSULE PRODUCTION





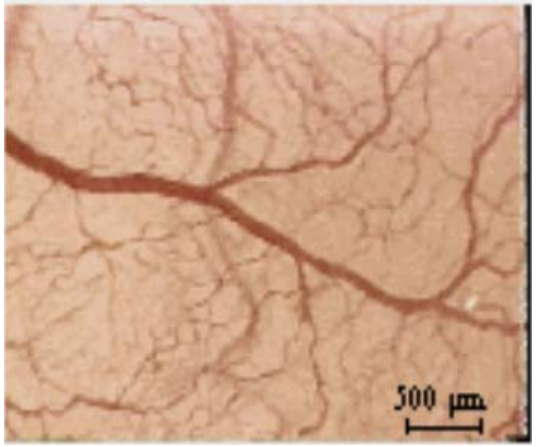
REPLIDERM Production

- Human Labor Needed
  - Minimum – 1PhD, 3 technical assistants
- Facility Layout (30,000sq-ft)
  - 1 cryo room, Storage, Offices, Animal storage, Laboratory testing, 2 Production rooms

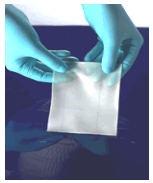


Quality Control

- 1% of all sheets produced to be selected at random and tested for quality assurances
  - All of sheets to be tested are halved. Half of each sheet are tested on a chorioallantoic membrane.
  - The remaining halves are tested in vitro with vascular endothelial cells

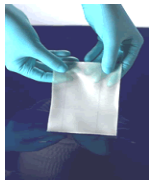


FDA PROCESS



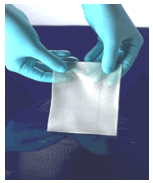
FDA Approval Process

- Most costly and time consuming step in bringing a new product to market.
- REPLIDERM is a Class III medical device. Class III medical devices are those that are implanted into a patient and left in the body.
  - Non-clinical testing
  - Manufacturing and facility testing
  - Clinical testing



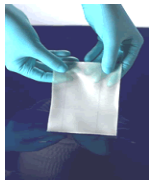
FDA Approval Process

- Modular Pre-Market Approval Process
  - Module 1: Non-clinical Trials
  - Module 2: Manufacturing & Facility Testing
  - Module 3: Human Clinical Trials



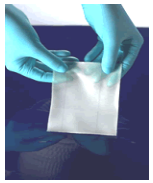
FDA Testing

- Historically FDA testing requires $200,000,000 to $300,000,000 and can last 10-15 years.
- It is this cost and time delay the FDA testing is the most critical step in bringing a new product to the market.



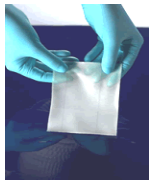
First Stage Variables

- A 1st Stage Variable is a decision that must be made before any production begins.
- For our project, we have two 1st Stage Variables:
  - The number of personnel to hire
  - The number of experiments to run before submitting our product to FDA evaluation.



Second Stage Variables

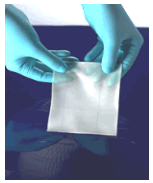
- A 2nd Stage Variable is a decision that is made after an outcome.
- For our project, we have several 2nd Stage Variables:
  - Each 2nd Stage Variable is a choice on whether or not to continue after an FDA Failure.
  - The chance of having an FDA Failure is dependent on the amount of tests conducted prior to FDA review.



First Stage Variable

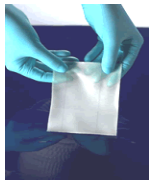
- Number of Personnel Options:
  - 1 Ph.D. and 3 Lab Technicians
  - 1 Ph.D. and 5 Lab Technicians
  - 1 Ph.D. and 7 Lab Technicians
- Number of Experiments to Run Prior to submission to FDA review:

Set	Cell Tests	CAM Tests	Nude Mice	Guinea Pigs	Pigs	Dogs
A	100	100	100	100	100	100
B	100	100	50	50	50	50
C	50	50	50	50	25	25



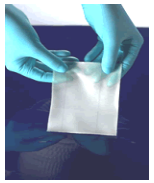
Second Decision (First Stage Variable)

Set	Description	Description
Set A	100 Cell Flask, 100 CAM, 100 Nude Mice, 100 Guinea Pig, 100 Pig, 100 Dog Tests	More time and money spent up front, but higher likelihood of passing FDA trials on 1st try.
Set B	100 Cell Flask, 100 CAM, 50 Nude Mice, 50 Guinea Pig, 50 Pig, 50 Dog Tests	Compromise on time and money, but the chances of passing FDA are less than A.
Set C	50 Cell Flask, 50 CAM, 50 Nude Mice, 50 Guinea Pig, 25 Pig, 25 Dog Tests	Lest costly, but higher likelihood of being forced to repeat some FDA trials.

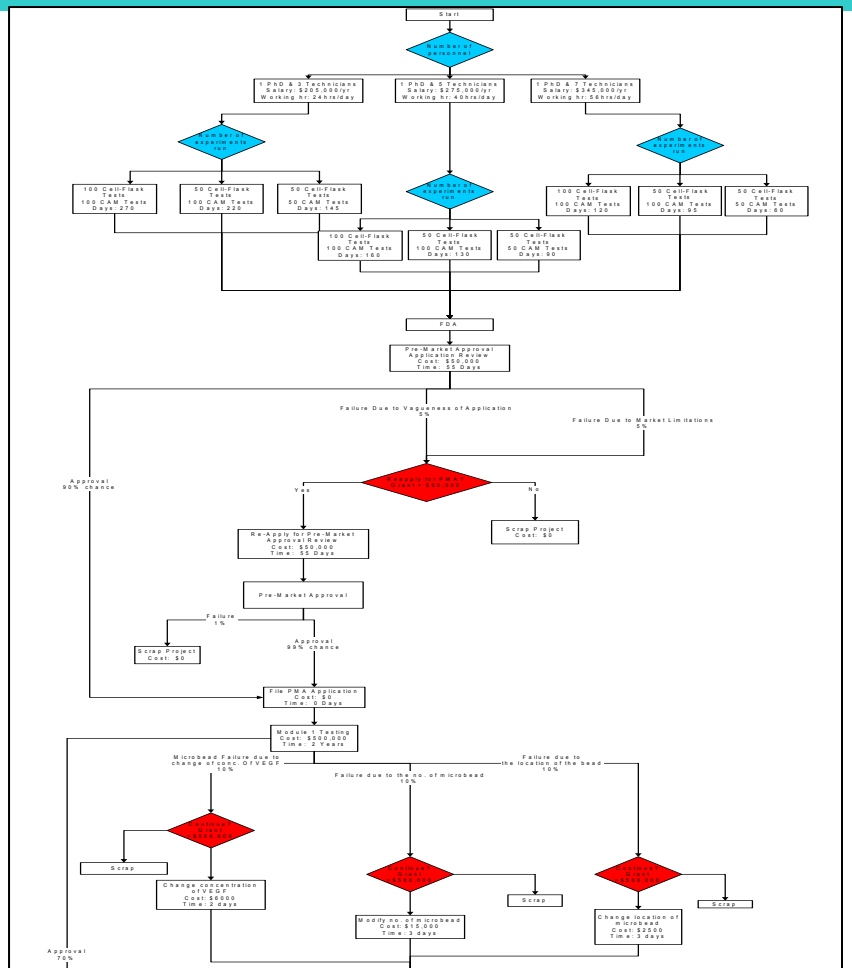


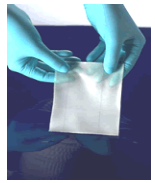
Initial Grant Money

- The initial amount of grant money that we obtain will be the deciding factor in which employment option and which testing option we choose.
- Initial grant money will be obtained from the NIH, NSF, CDC, and other various government granting agencies.

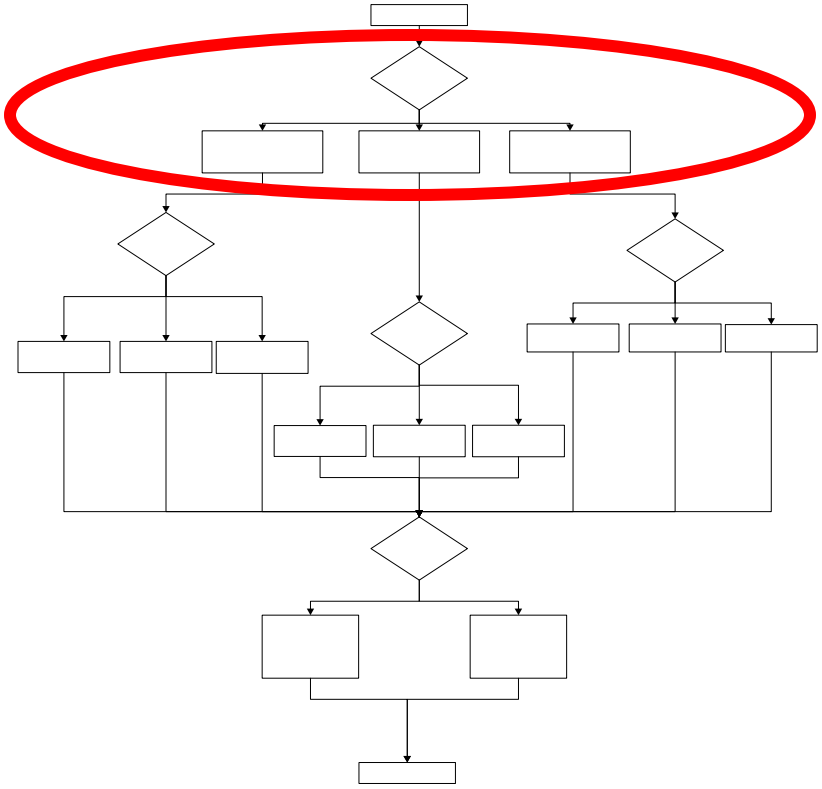


FDA APPROVAL

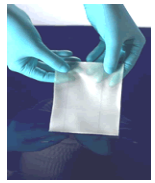




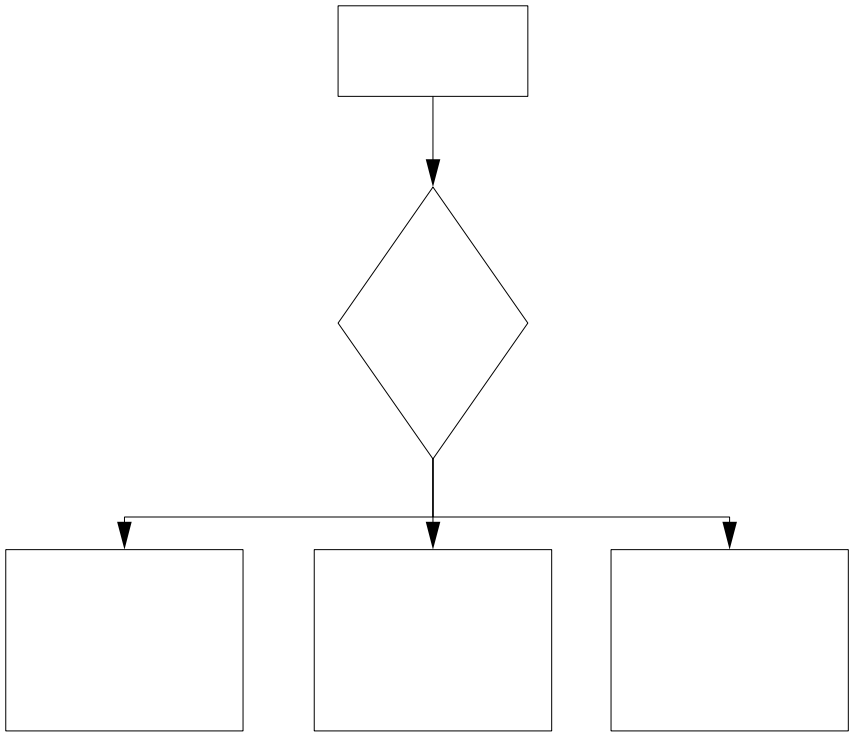
First Decision (First Stage Variable)



1 PhD & 3 Technicians
Salary: $170,000/yr
Working hr: 24hrs/day

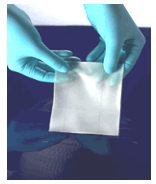


Selection of Employees

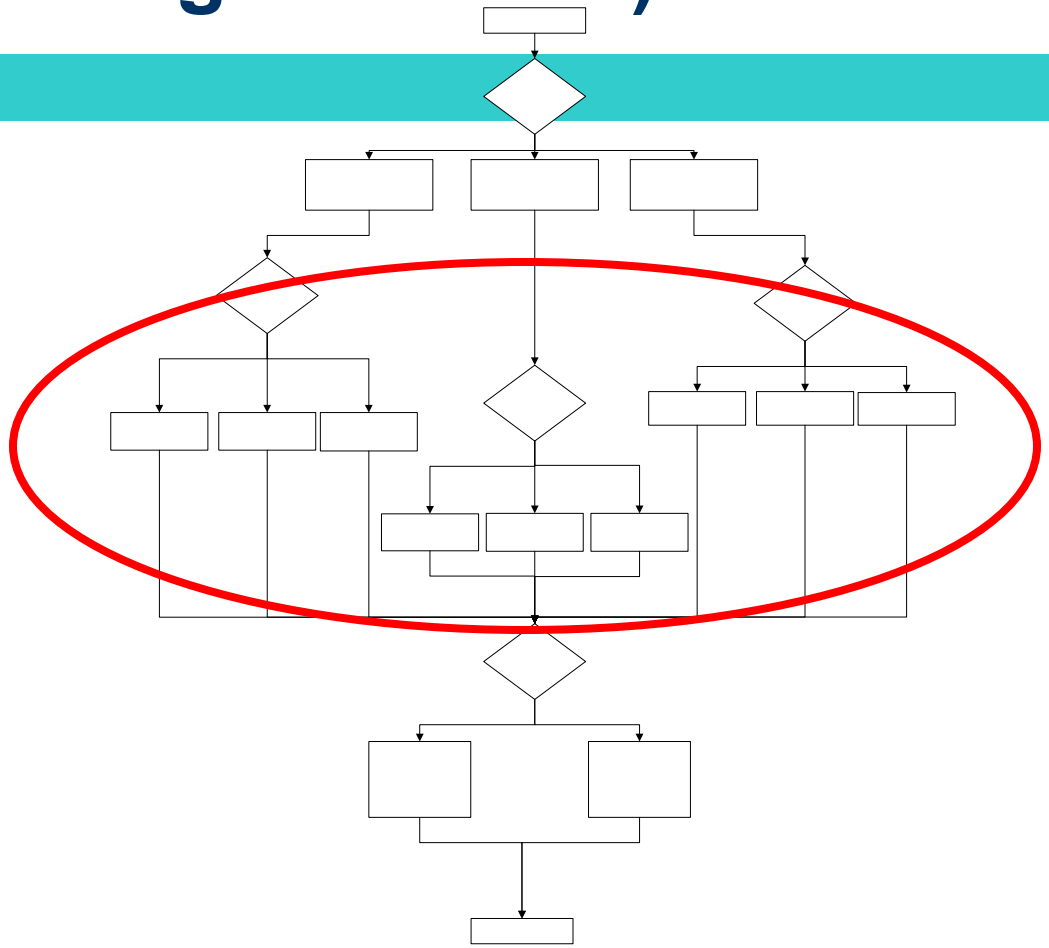


- Decision is based on the amount of initial grant money available.
- The more technicians the shorter the time required to run the same amount of test.

Start



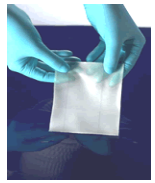
Second Decision (First Stage Variable)



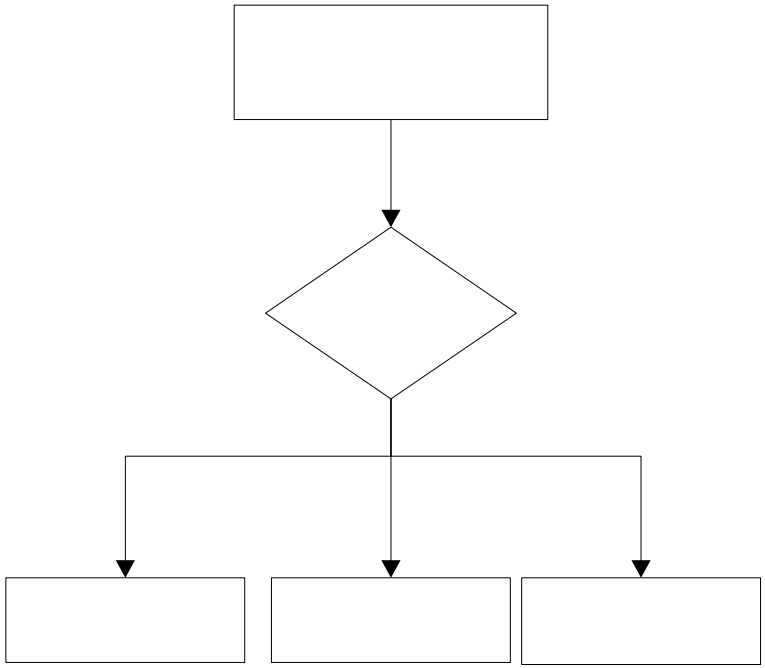
1 PhD & 3 Technicians
Salary: $170,000/yr
Working hr: 24hrs/day

1 PhD
Sala
Worki

Number of experiments

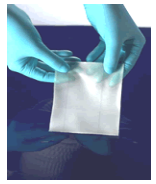


Selection of Experiments

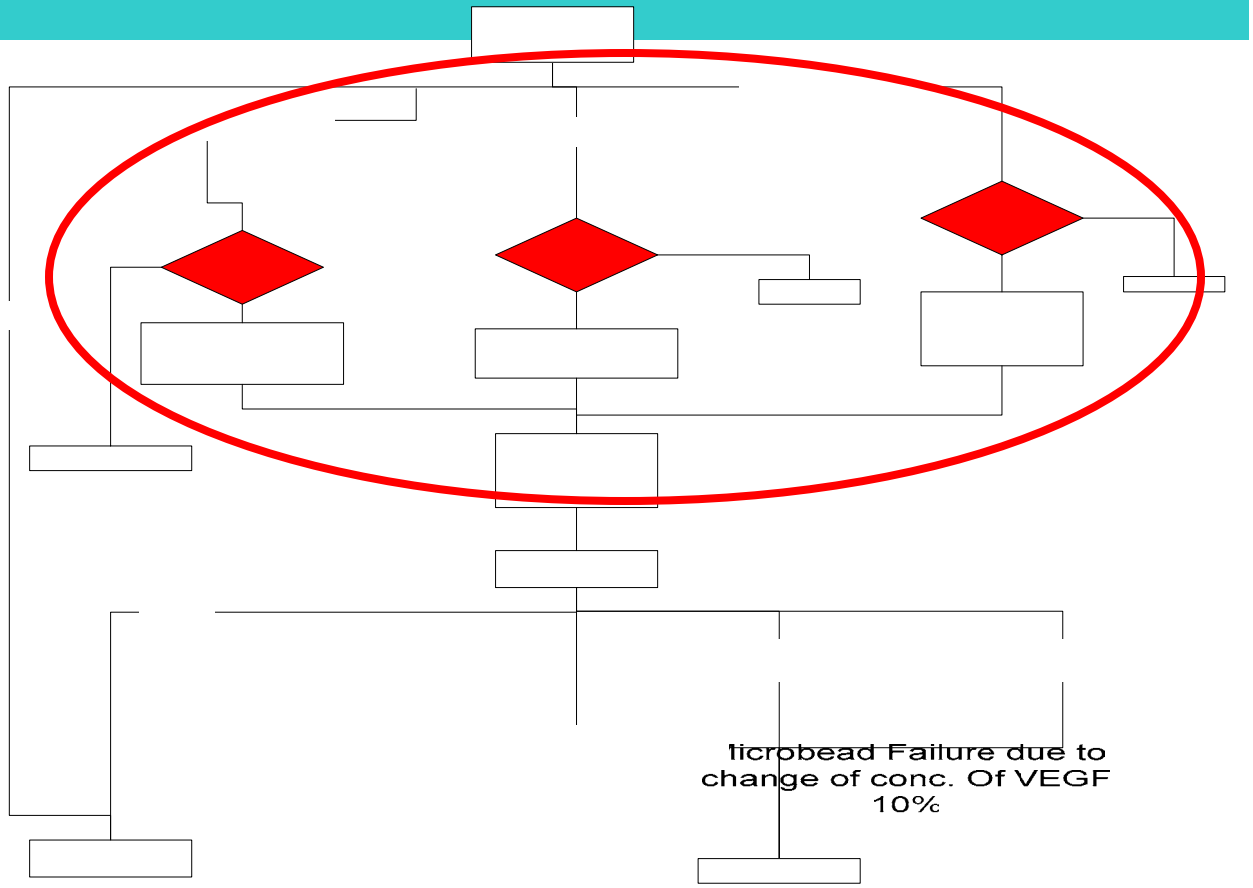


- Set A - more experiments run concurrently, more in-depth testing and increasing the chances of passing the FDA trials on the 1st try.
- Set C - costs the least, begins the FDA testing quicker, but a higher likelihood of failure.
- All sets of experiments perform the same types of tests.

1 PhD & 3 Technicians
Salary: $205,000/yr
Working hr: 24hrs/day

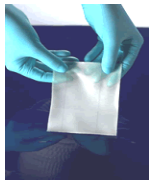


Failure in FDA Approval (Second Stage Decision)

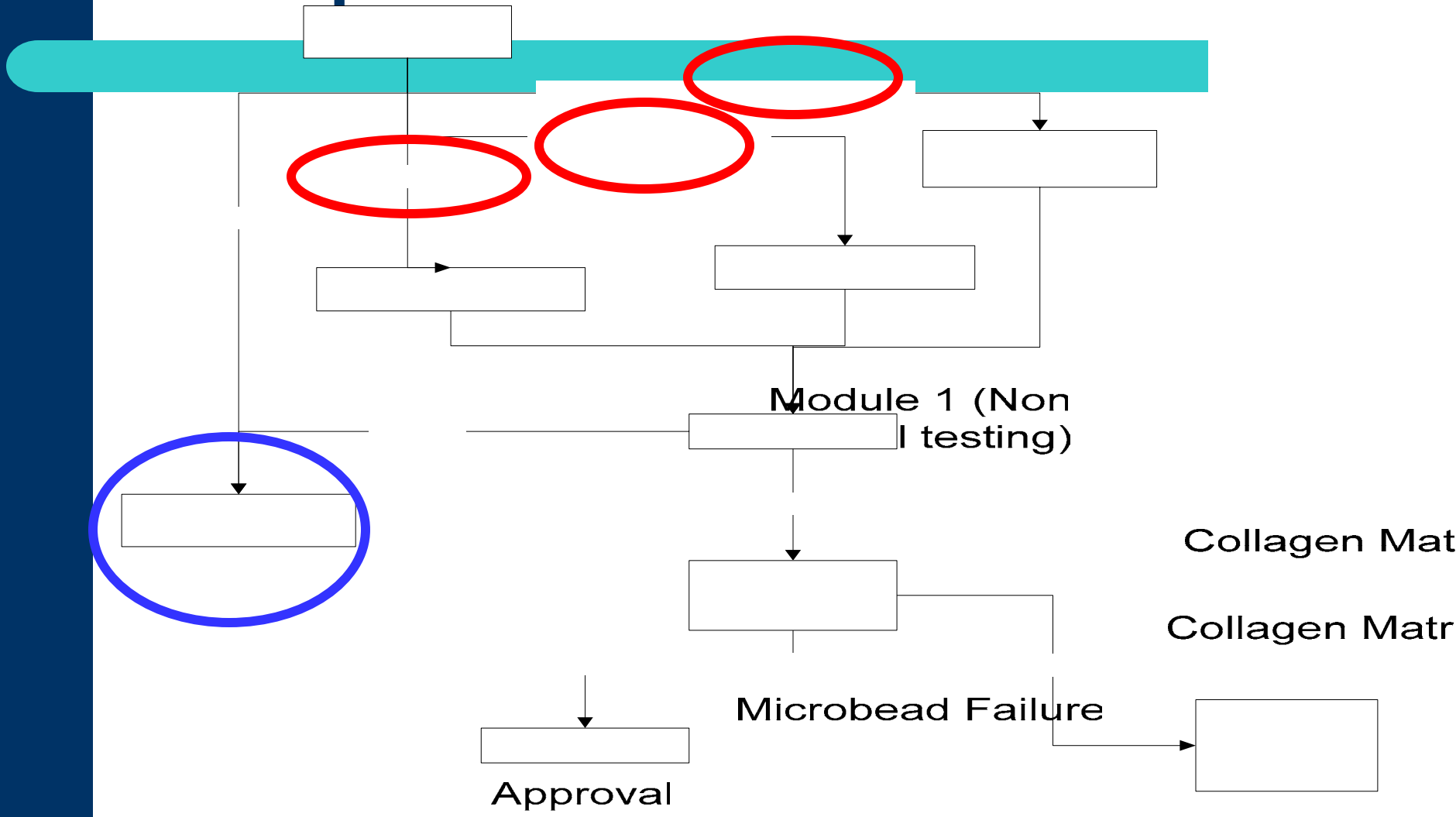


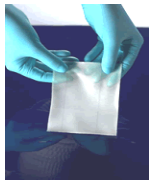
Module 1
Cost: $5
Time: 2

Failure due to th



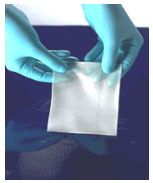
Example: Module 1 Failure



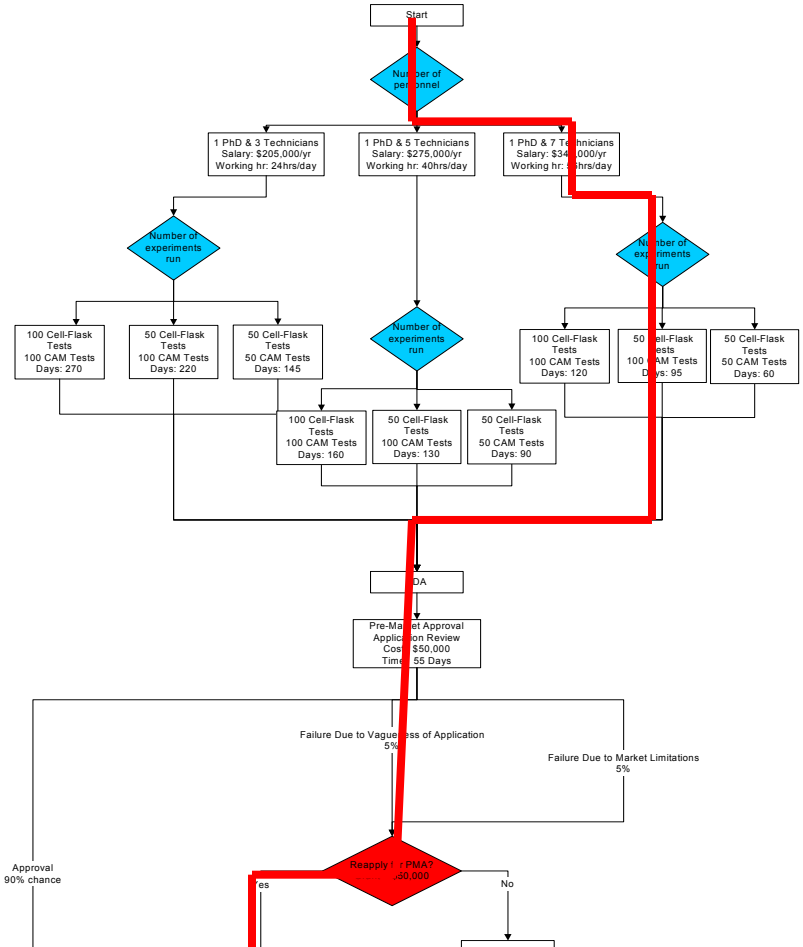


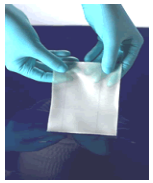
Fixing a Failure with the Concentration of VEGF in the Microbeads

- Cost of Fixing:
  - $12,000 total
  - $6,000 for beads themselves
  - $2,000 for cell and CAM tests
  - $2,000 for small animal tests
  - $2,000 for labor
- Time required is 14 days:
  - Cell, CAM, and small animal tests will be run concurrently



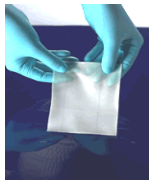
Example: Pathway



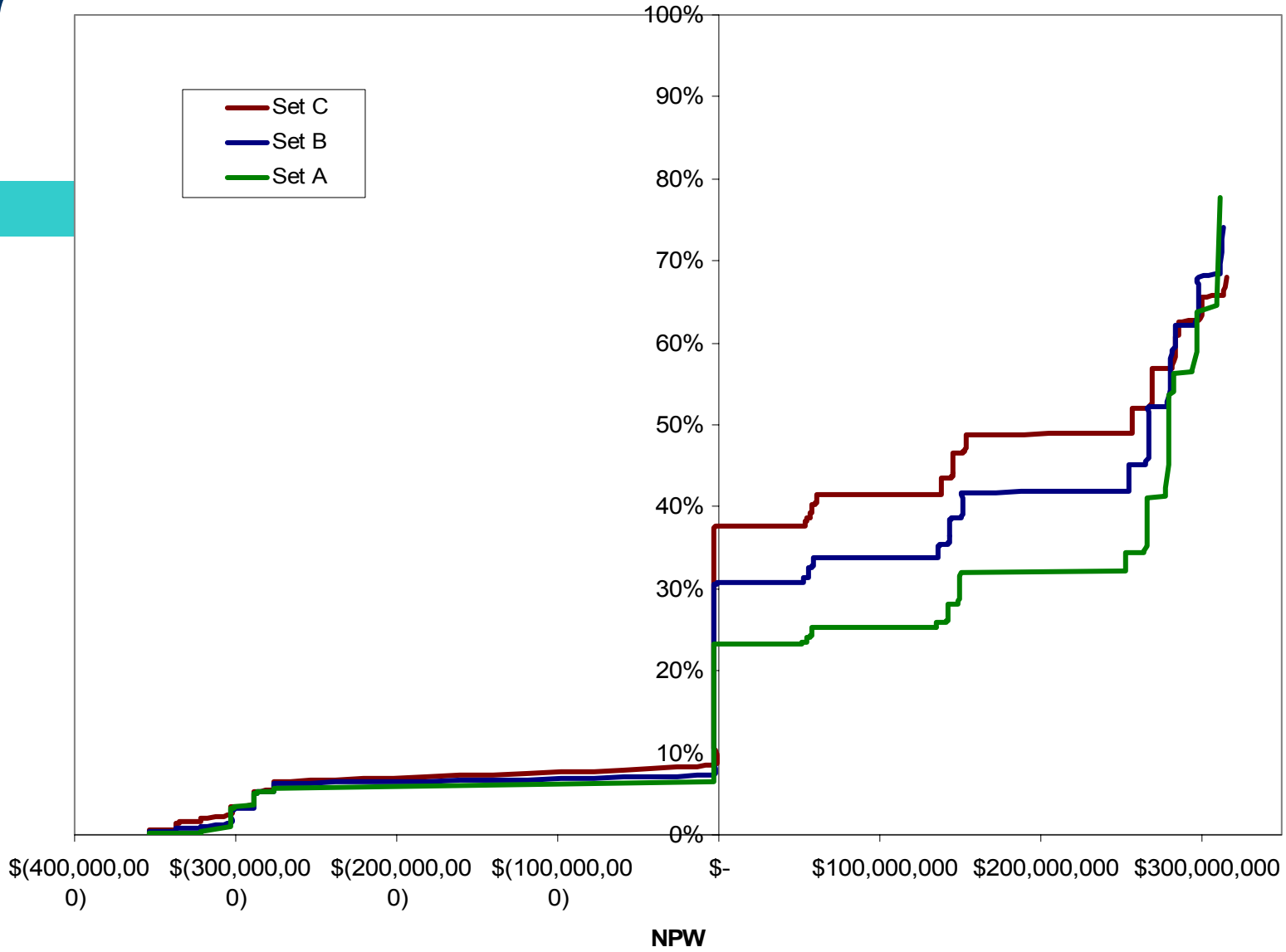


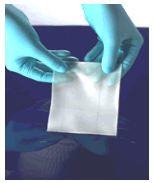
FDA Decision

- 9 decisions
- Each decision contains 738 pathways
- Total pathways: 6642 pathway
- Calculated by Excel
- Each pathway contains its cost, duration and probability

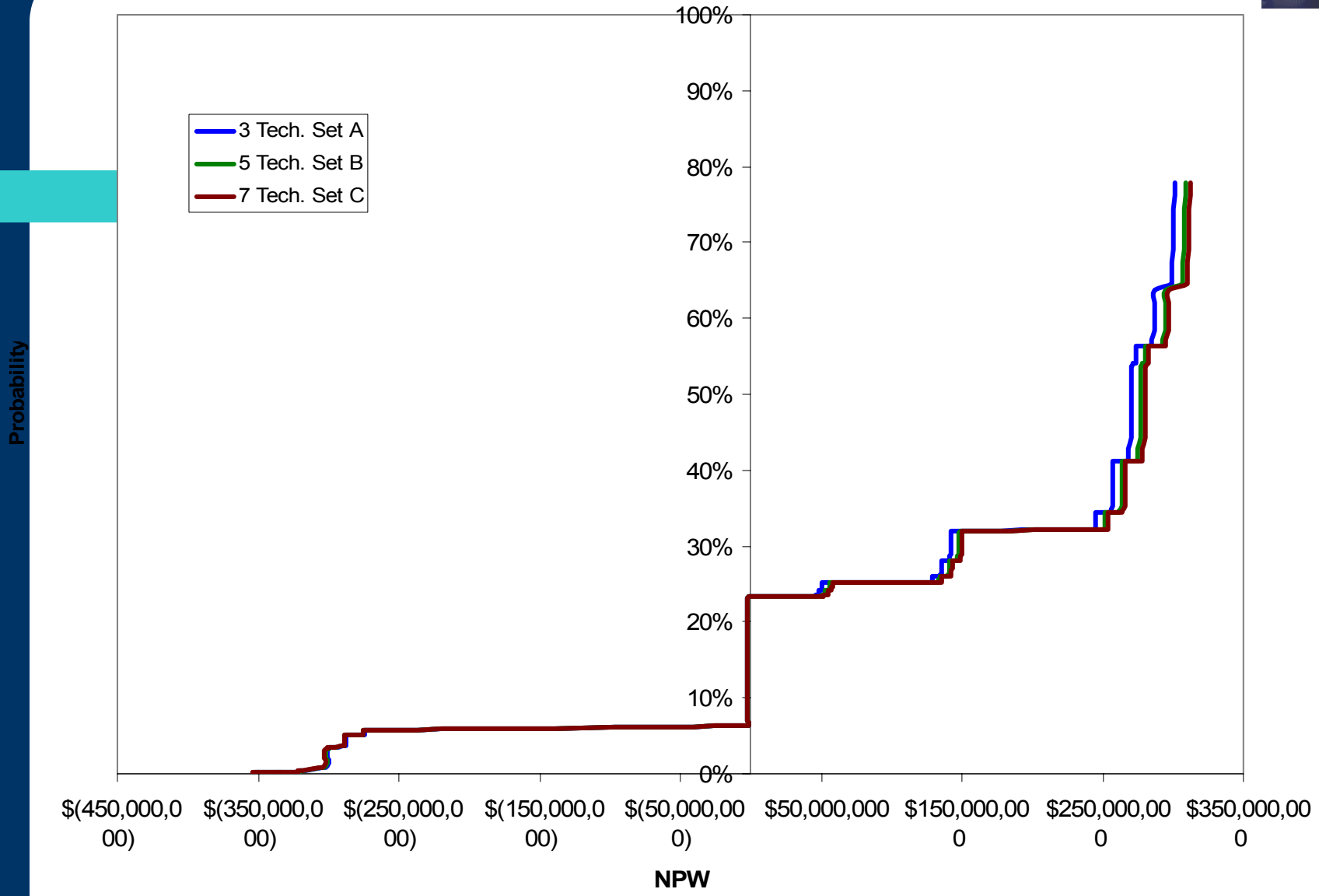


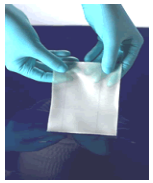
Comparison of different set of experiments





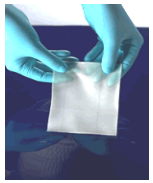
Comparsion of different number of personnel





Option to Chose

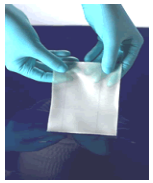
- 1 Ph.D. and 7 technicians
- Perform test set A



Justification

- Different kinds of failure may occur.
- The easiest problem to fix is one that does not occur.
- Costs escalate rapidly with every time a product must be re-evaluated by the FDA.

BUSINESS PLAN



Cost Evaluation

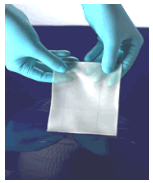
- Direct cost - $ 8,960,000

  Equipment cost, Installation cost, Building & facility cost, Service charges, Raw material cost, Quality control

- Indirect cost - $ 350,120,000

  FDA cost, Engineering and supervision

FCI → $ 359,079,000

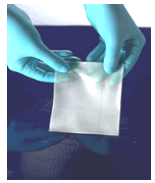


Business Goal

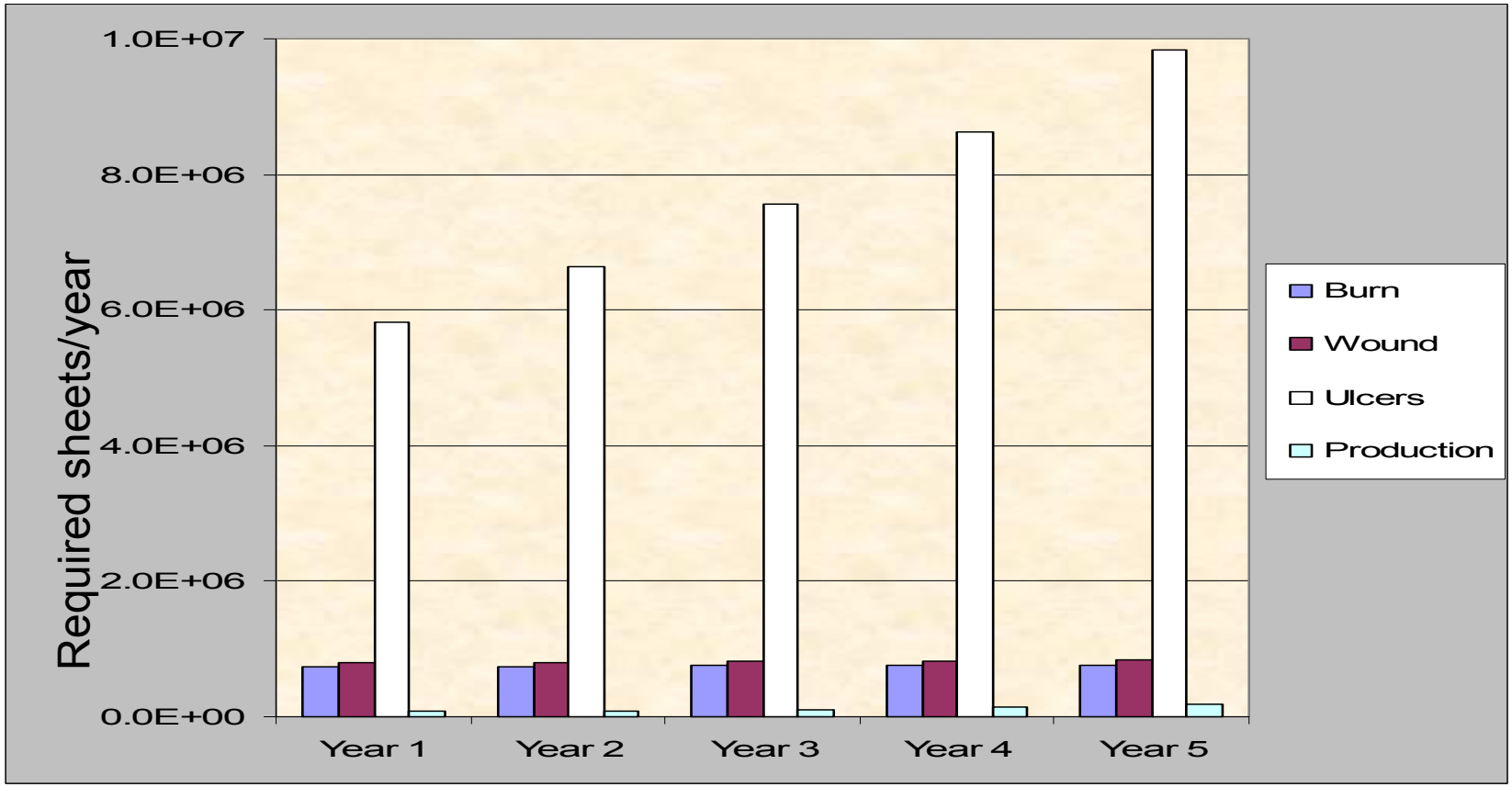
- Obtain the major part of research cost from following sources

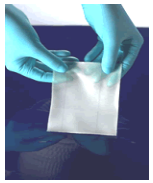
  - NIH, NSF, CDC

- Production of new allograft Repliderm with the rate of 2220 sheets/month
- Breakeven in 2-3 years



Demand in the Market

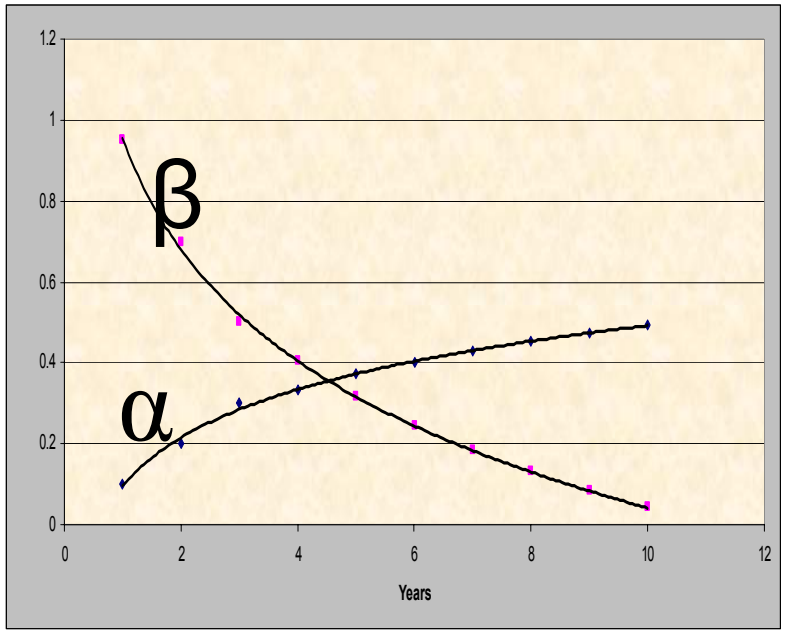




Current Market Demand

- Market Demand Model

$$\beta\,(t, x)\, p_1 d_1 = p_2 (D - d_1)\ \alpha\,(t, x)$$



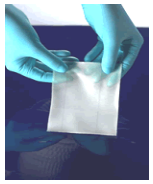
D – Total Production Demand – 500,000

d_1 – *REPLIDERM* Demand

p_1 – *REPLIDERM* Price/sheet

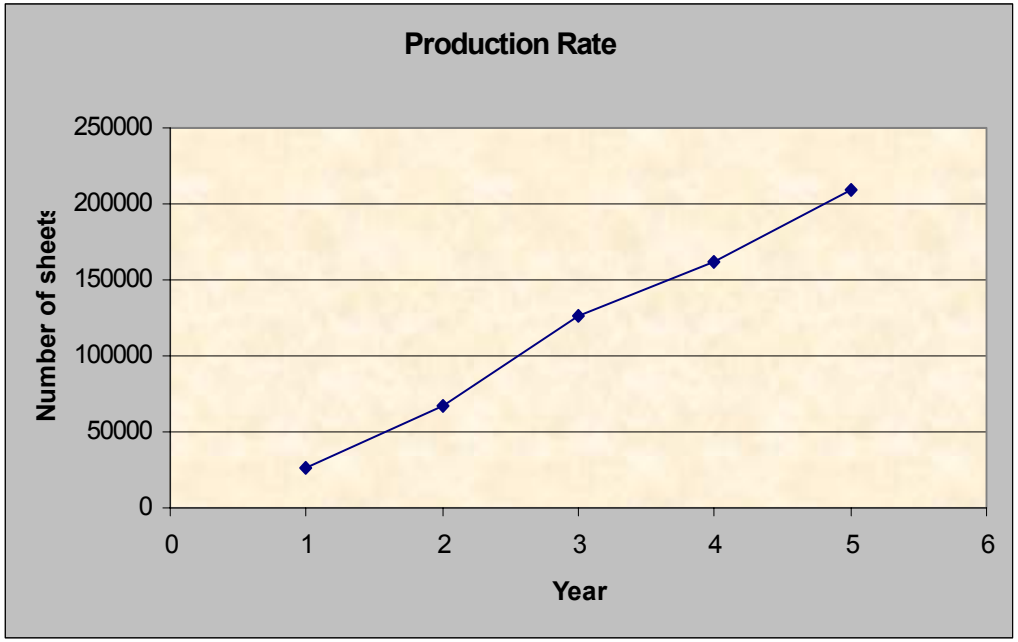
p_2 – Competitor's Price/sheet

x - Marketing



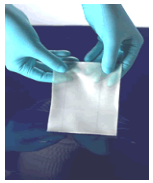
Production rate & sale price

$$\sum_{i=1}^{3} p_1 d_{1i} - PC = FCI$$



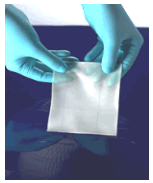
Product price = $ 1870 / sheet

Production rate = 2220 sheets / month (1st yr)



Marketing

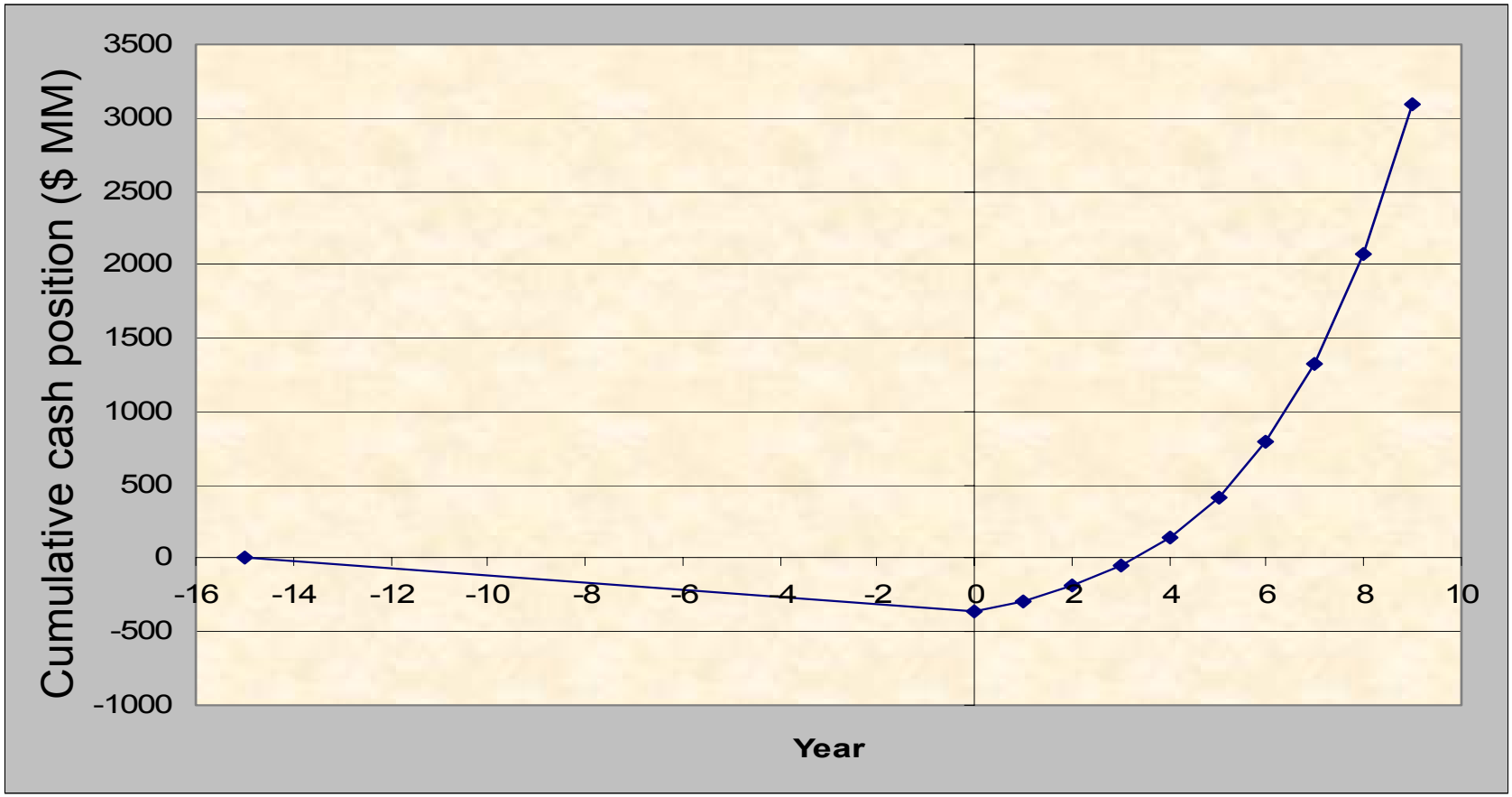
- Product distribution
  - 56 hospitals every six months
- 3 national conferences annually
- 2 International conferences annually
- Tradeshows and fellowship

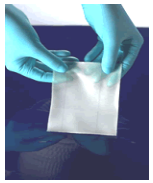


Cumulative Cash Position

- Increase in production rate following the model
  - Initially 26645 sheet / year
- Increase in staff by 25%
- Increase Marketing by 10-20%

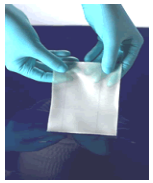
Cumulative Cash Position Forecast





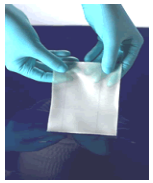
Location Selection

- Factors considered
  - NIH funding
  - Employment in Biotech companies
  - Cost of living
  - Number of private biotech companies
  - Number of Hospitals
  - Corporate tax rate
- Fairfield, CA



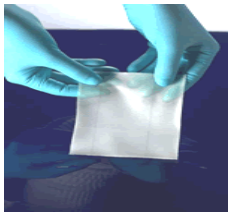
Conclusion

- Control release delivery system
- Pre-FDA testing by 8 personnel
- Testing Set A
- Sale price $1870 / sheet
- Production rate 27000 sheets / year



Acknowledgements

- Dr. Bagajewicz
- Dr. Sikavitsas
- Dr. Yannas (Integra LifeScience)
- Timothy King and Charles Patrick (University of Texas)



QUESTIONS?????