

# 2011 Midwest ISLFD Meeting

International Society of Lyophilization – Freeze Drying  
April 14, 2011

## *Lyophilization of Parenterals: History and New Horizons*



**Edward Trappler**

**Lyophilization Technology, Inc**

# *In Appreciation!*

*ISL-FD*

*Robert Sever, Praxair*

*Kevin Tebrinke, Scientific Protein Labs*

*Timothy McCoy, Ben Venue Labs*

*Mark Meluso, Key Scientific, SP Industries*

# *Thanks!*

*To my associates at LTI*

*who make extraordinary things happen.*

*Andrew Smith, Development Sciences*



# *Introduction*

## *Examples of Lyophilized Products*



**Back to the Future**

**AICs**

**siRNA**

**"Gardasil Effect"**

# **Back to the Future**

**VLPs**

**replikins**

**Microneedles**

**"Factory in a box"**

# ***Past, Present and Future***

## **Lyophilized Parenteral Products**

- ✦ Early endeavors: Pre-1938
- ✦ The next 44 years: Pre-1982
- ✦ Explosion in growth: To 1994
- ✦ Through the millennium: since 1994
- ✦ Future horizons: Products and Delivery

# ***Historical Perspective***

## **Legacy Lyophilized Products**

- 1929** The preservation of yellow fever virus  
Journal of Experimental Medicine, 50, 1-13
- 1938** The preservation and concentration of human serums for clinical use  
Journal of the American Medical Association, 107, 956-959

# ***Early Endeavors***

- ✦ **Blood Plasma Products**
- ✦ **Antibiotics**
- ✦ **Vaccines**

# ***Early Endeavors***

## **Blood Plasma Products**

- ✦ Plasma (Sharp & Dohme Company / Max Strumia, Bryn Mawr University)

“... a fine golden-yellow powder that remained sterile for years yet became fully reconstituted with the addition of water.”

**(Blood, Douglas Starr, 1998)**

# ***Early Endeavors***

## **Blood Plasma Products**

- ✦ Hemin (Panhematin, Abbott, anemia)
- ✦ Corticotrophin (Acthar, MS Park-Davis, Rorer, Adrenal function – Herpes, Lupus )

# ***Early Endeavors***

## **Antibiotics**

- ✦ Penicillin G Procaine (Wycillin, Wyeth)

# ***Early Endeavors***

## **Vaccines**

- ✦ Measles, Mumps, Rubella, pertussis, swine erysipelas, diphtheria toxoid, tetanus toxoid, poliomyelitis

# ***The Next 44 Years***

▶ Plasma Products

▶ ***Antibiotics***

▶ Vaccines

▶ ***Oncolytics***

▶ ***Critical care products***

# ***The Next 44 Years***

## **Antibiotics**

### ✦ Amino-glycosides

Tobramycin Sulphate (Nebcin, Lilly, Top 300)

### ✦ Cephalosporins

Cephalixin (Keflex, Lilly, Top 100, >\$100m )

Cefozolin (Ancef, Kefzol, SKB, Lilly)

# ***The Next 44 Years***

## **Antibiotics**

### ✦ **$\beta$ -Lactams**

Vancomycin HCl (Vancocin, Lilly, Top 100, >\$100m)

### ✦ **Tetracyclines**

Doxycycline (Vibramycin, Pfizer, Top 200, > \$100m)

# ***The Next 44 Years***

## **Vaccines**

Infectious bronchitis virus

(IBV H-52, H-120, N strains)

“Stability of Live, Freeze-Dried Virus Vaccines” in  
Proceedings of the International Symposium  
on Freeze-Drying of Biological Products,  
Washington DC 1976 J. Peterman's,  
Recherche et Industrie Therapeutiques,  
R.I.T. Rixensart, Belgium

# ***The Next 44 Years***

## ***Oncolytics***

- ✦ Dactinomycin, (Cosmegen, Merck)
- ✦ Cisplatin (Plantinol, BMS, Top 100, >\$100m)

# ***The Next 44 Years***

## **Critical care products**

- ✦ Dantroline Na (Dantrium IV , P&G, Top 800, P&G)



# ***The Next 44 Years***

## **Corticosteroids**

- ✦ Hydrocortisone Na Succinate (Solu-Cortef, Upjohn)
- ✦ Methylprednisolone Na Succinate (Solu-Medrol, Upjohn)

# ***Explosion in Growth***

✦ Plasma Products

✦ ***Anti-infectives***

***Antibiotics***

***Antivirals***

✦ Vaccines

✦ ***Oncolytics***

✦ ***Critical care products***

# ***Explosion in Growth***

## **Antibiotics**

### ✦ $\beta$ -Lactams

Aztrenam (Azactam, BMS, 1986, Top 100 >\$100m)

### ✦ Cephalosporin

Cephalixin (Keflex, Lilly, Top 100, >\$100m)

### ✦ Combination products

( $\beta$ -lactam/cephalosporin, G+/G-)

Imipenem/Cilastatin, Merck, 1985, Top 100, >\$500m

# ***Explosion in Growth***

## ***Antivirals***

- ✦ Ganciclovir (Cytovine, Syntex/Roche), 1989, Top 300)
- ✦ Acyclovir (Zovirax, GSK, 1982, Top 100, >\$1b)
- ✦ Interferon  $\alpha$ -2A (Roferon-A, 1986, (Roche) Top 300)
- ✦ Interferon  $\alpha$ -2B (Intron-A, Schering, Top 100, >\$500m)

# ***Through the Millennium***

- ✦ Plasma Products
- ✦ **Anti-infectives**
  - Antibiotics (**MRSA**)
  - Antivirals
- ✦ **Vaccines**
- ✦ Oncolytics
- ✦ Critical care products

# ***Through the Millennium***

## **Oncolytics**

✦ Trastuzumab (Herceptin IV, Genentech, 1998)

# ***Through the Millennium***

## **Critical care products**

- ✦ Interferon  $r\beta 1b$ , (Betaseron, Bayer, 1993)
- ✦ Alteplase (TPA) (Actavase, Genentech/Roche, 2002)

# ***Future Horizons***

- ✦ Plasma Products
- ✦ **Anti-infectives**
  - Antibiotics (**MRSA**)
  - Antivirals
- ✦ **Vaccines**
- ✦ Oncolytics
- ✦ Critical care products

# ***Future Horizons***

## **Lyophilized Parenteral Products: Late Stage Antibiotics (MRSA)**

- ✦ Telavancin (Astellas/Theravance)
- ✦ Medocaril (Ceftobiprole, J&J/Basilea)

# ***Future Horizons***

## **Vaccines**

- ✦ HPV (Ceravix, GSK, EU)
- ✦ DPT + polio and Haemophilus influenza b  
(Pentacel, Sanofi-Pasteur, 2008)
- ✦ Pneumoccal (Prevnar, Wyeth)
- ✦ Herpes Zoister (Zostav, Merck)

“Momentum Builds in Vaccine Development”, Angelo DePalma,  
Pharmaceutical Commerce, Vol 4 #4, May 2009

# ***Future Horizons New Vaccines***

## **Cancer vaccines in Phase II trials**

- ✦ Advaxis (live listeria)
- ✦ Trangene

“World market for cancer vaccines 2007-2012, Visiongain 17/01/2007

# ***Future Horizons New Vaccines***

## **Cancer vaccines in Phase III trials**

- ✦ **GVAX**
- ✦ **PANVAC-VF**
- ✦ **Alloverctin7**
- ✦ **Stimuvax**

“World market for cancer vaccines 2007-2012, Visiongain 17/01/2007

# ***Future Horizons Oncolytics***

## **Oncolytics**

- ✦ Fifth-largest therapeutic class (Worldwide sales)
- ✦ Oncology market is expanding

Monoclonal Antibodies in Cancer Therapy Report 2009-2024, Visiongain 05/07/09

# ***Future Horizons Oncolytics***

## **Growth of Parenteral Oncolytics**

- ✦ 1998: 12 in top 200 of world medicines
- ✦ 2008: 23 in top 200 of world medicines  
***3 products in top 10 medicines.***

# *Future Horizons*

## *mAbs as Oncolytics*

### **Oncolytics**

- ✦ Worldwide oncology market is fifth largest therapeutic class.
- ✦ Totaled a \$66b market in 2007
- ✦ Top 10 therapies total 35% of market revenue
- ✦ A total of 48 companies pursuing therapies

Monoclonal Antibodies in Cancer Therapy Report 2009-2024, Visiongain 05/07/09  
Therapeutic Monoclonal Antibodies Report 2008-2023, Visiongain 25/07/08

# ***Future Horizons mAbs as Oncolytics***

## **Oncology market is expanding**

- ✦ Rituxan/MabThera
- ✦ Avastin
- ✦ Herceptin
- ✦ Erbitux
- ✦ Vectibix
- ✦ Campath
- ✦ Mylotarg
- ✦ Zevalin and Bexar

Monoclonal Antibodies in Cancer Therapy Report 2009-2024, Visiongain 05/07/09  
Therapeutic Monoclonal Antibodies Report 2008-2023, Visiongain 25/07/08

# ***Future Horizons Biopharmaceuticals***

**Biotechnology is major growth of products.**

**2005 - FDA approved 54 biopharmaceuticals.**

**2007 - Global product market was >\$75b.**

**Top 10 selling biopharmaceuticals > 50%  
total biotech drug sales in 2007.**

**2008 - Revenues reached ~\$125b**



“Global Biotech Market Analysis and Forecasts 2008-2023”, Visiongain, 26/08/2008, “Biosimilars and Follow-on Biologics Report: The Global Outlook 2009-2024” Visiongain, 09/04/2009, and “Antibody Therapeutics: Triumphs and Tribulations”, American Biotechnology Laboratory, Vol 27,#8 August 2009.

# ***Future Horizons Biopharmaceuticals***

- ✦ **Biologics continue to outperform “Small Molecules”.**
- ✦ **Patents for many biologicals have or will soon expire.**
- ✦ **Branded products face increasing biosimilar competition, market takes off.**
- ✦ **Biosimilars will face competition from newer branded biologics.**

“Biosimilars and Follow-on Biologics Report: The Global Outlook 2009-2024” Visiongain,  
09/04/2009

# ***Future Horizons Biopharmaceuticals***

## **Top 10 Biopharmaceuticals**

Enbrel

Procit/Epro

Aranesp

Herceptin

Remicade

Epogen

MabThera/Rituxan

Avastin

Neulasta

Humira

“Global Biotech Market Analysis and Forecasts”, 2008-2023 Visiongain, 26/08/2008

# ***Future Horizons Biopharmaceuticals***



## **Top biopharmaceuticals in 2007**

“Blockbuster” Monoclonal antibody (mAb) therapeutics

Remicade

TNF- $\alpha$

\$6.5b

Herceptin

Her2

\$4.8b

“Antibody Therapeutics: Triumphs and Tribulations, American Biotechnology Laboratory,  
Vol 27,#8 August 2009

# ***Future Horizons Biopharmaceuticals***



## **Potential “Blockbuster” therapeutics**

Cimzia (UCB) PEGlated Fab'/anti-TNF- $\alpha$

Actemra (Roche) anti IL-6 receptor

Stelera (BMS/Medarex) anti L12 IL-23

# ***Future Horizons Products Becoming Generic***

## **Products Coming Off Patent to 2013**

- ✦ **Oncolytics: (more than 35% of products)**
- ✦ **Anti-infectives (23%)**
- ✦ **CNS (16%)**
- ✦ **Cardiovascular (9%)**

In *Injectable Generic Drugs: Prospects & Opportunities to 2013*, Karen Holmes, Espicom, July 18, 2008.

# ***Future Horizons***

## ***Products Becoming Generic***

### **Oncolytic Products off Patent**

- ▶ Paraplatin (carboplatin, BMS)  
(11 generic companies filing ANDAs)

# ***Future Horizons***

## ***Products Becoming Generic***

### **CNS (MS and Schizophrenia)**

- ✦ Intron A (Schering-Plough )
- ✦ PEGIntron (Schering-Plough )
- ✦ Betaferon ( $\beta$ -interferon) (Burlex)

# ***Future Horizons Products Becoming Generic***

## **Cardiovascular Products**

✦ Flolan (epoprostenol, GSK )

# ***Future Horizons Products in Development***

- ✦ Plasma Products
- ✦ **Anti-infectives**
  - Antibiotics (**MRSA**)
  - Antivirals
- ✦ **Vaccines**
- ✦ **Oncolytics**
- ✦ **Critical care products**

# ***Future Horizons***

## ***Vaccines in Development***

### **Infection, viruses and cancer**

- ✦ Hepatitis viruses
- ✦ HIV
- ✦ Human papilloma
- ✦ Epstein-Barr
- ✦ Human T-cell leukemia
- ✦ *Helicobacter pylori*

“World market for cancer vaccines 2007-2012, Visiongain 17/01/2007

# ***Future Horizons Vaccines in Development***

## **Therapeutic Vaccines**

- ✦ Whole-cell
- ✦ Gene modified
- ✦ Dendritic cell
- ✦ Peptides
- ✦ Bacterial vector
- ✦ Heat-shock protein
- ✦ Viral vector
- ✦ DNA

# ***Future Horizons Vaccines in Development***

## **Investigators and investors in vaccines**

- ✦ **Investing/Investigating Companies: 37**
- ✦ **Investigating Research Centers: 25**

“World market for cancer vaccines 2007-2012, Visiongain 17/01/2007

# ***Future Horizons Vaccines in Development***

## **Infections needing vaccines**

- ✦ Dengue
- ✦ Epstein-Barr (EBV)
- ✦ Hepatitis C
- ✦ Hepatitis E
- ✦ HIV/Aids
- ✦ Malaria

“The Global Vaccines Market 2008-2023”, Visiongain 17/01/2007

# ***Future Horizons Vaccines in Development***

## **Infections needing vaccines**

- ✦ West Nile virus
- ✦ Helicobacter pylori
- ✦ Nosocomial
- ✦ Respiratory
- ✦ Roundworm
- ✦ Hookworm

“The Global Vaccines Market 2008-2023”, Visiongain 17/01/2007

# ***Future Horizons Vaccines in Development***

## **Vaccine developments needed**

- ✦ Single vaccine effective against more strains
- ✦ A universal influenza vaccine
- ✦ An improved tuberculosis vaccine

“The Global Vaccines Market 2008-2023”, Visiongain 01/09/2008

# ***Future Horizons Vaccines in Development***

## **Diseases needing vaccines**

- ✦ Cancer
- ✦ Tobacco

“The Global Vaccines Market 2008-2023”, Visiongain 17/01/2007

# ***Future Horizons***

## ***Vaccines in Development***

### **Cancer Vaccines**

- Prophylactic
- Therapeutic

# ***Future Horizons Vaccines in Development***

## **Types of Prophylactic Vaccines**

- ✦ Live, attenuated
- ✦ Recombinant live
- ✦ Inactivated
- ✦ Toxoid
- ✦ Subunit
- ✦ Conjugate
- ✦ Recombinant subunit
- ✦ DNA
- ✦ Recombinant vector

# ***Future Horizons Vaccines in Development***

## **Cancer Vaccines**

- ✦ Prophylactic – Prevent infection by cancer causing viruses, such as:
  - hepatitis B virus (HBV) – liver cancer
  - human papilloma virus (HPV) – cervical cancer
  - Gardasil (Merck) Cervarix (GSK)
- ✦ Therapeutic – Treat existing cancer by stimulating the immune system:
  - Provenge – (Dedreon, April 2010)***
  - First therapeutic vaccine for cancer.***

# ***Future Horizons Vaccines in Development***

## **Progress in vaccine developments**

- ✦ Manufactures are expanding scope of vaccines
- ✦ Next generation vaccines
- ✦ Novel adjuvants in development
- ✦ New vaccine delivery mechanisms and formulations
- ✦ Brand manufacturers will not face significant generic competition

“The Global Vaccines Market 2008-2023”, Visiongain 01/09/2008

# ***Future Horizons Vaccines in Development***

## **Challenges in vaccine development**

- ✦ Lengthy and expensive R&D
- ✦ Extensive clinical studies and regulatory review
- ✦ High cost and long lead times of conventional manufacturing

“The Global Vaccines Market 2008-2023”, Visiongain 01/09/2008

# ***Future Horizons mAbs in Development***

## **Monoclonal Antibodies: mAbs**

- ✦ Growing at double digit rates
- ✦ Central products of biotechnology
- ✦ treatments for
  - cancer
  - autoimmune
  - inflammatory
- ✦ Most active and promising pipelines

# ***Future Horizons mAbs in Development***

## **Monoclonal Antibodies: mAbs**

- ✦ 1998: two drugs on world market
- ✦ 2008: 21 FDA approved therapies  
8 blockbuster drugs  
(2007: \$21.9bn)
- ✦ 2008 to 2023: leading biotech product

— Therapeutic Monoclonal Antibodies Report 2008-2023, Visiongain 25/07/08

# ***Future Horizons mAbs in Development***

## **“Big 5” Monoclonal Antibodies**

- ✦ Remicade
- ✦ Rituxan
- ✦ Herceptin
- ✦ Avastin
- ✦ Humira

# ***Future Horizons mAbs in Development***

## **“Top 7” growing Monoclonal Antibodies**

- ✦ Cimzia (UCB)
- ✦ Golimumab (J&J)
- ✦ Denosumab (Amgen)
- ✦ Numax (AstraZeneca/Medimune/AME)
- ✦ Bapineuzumab (Elan/Wyeth)
- ✦ ABT-874 (Abbott)
- ✦ Ustekinumab (J&J)

# ***Future Horizons mAbs in Development***

## **Emerging Monoclonal Antibodies**

- ✦ Erbitux (Merck/Imclone)
- ✦ Lucentis (Roche/Genentech)
- ✦ Synagis (AstraZeneca)

# ***Future Horizons mAbs in Development***

## **Future of Monoclonal Antibodies**

- ✦ Potential for leading therapeutic class
- ✦ One of strongest areas in Pharma
- ✦ Oncology is key driver to growth
- ✦ Near future: Humanized mAbs
- ✦ Long term: Fully human mAbs

# ***Future Horizons Products in Development***

## **Top 10 Therapy Classes**

- ✦ Erythropoietins
- ✦ Oncolytics
- ✦ Human Insulin
- ✦ Autoimmune
- ✦ Interferons
- ✦ Immunostim
- ✦ Immunosuppressives
- ✦ Growth Hormones
- ✦ Blood Factors
- ✦ Vaccines

“Global Biotech Market Analysis and Forecasts”, 2008-2023 Visiongain, 26/08/2008

# ***Future Horizons Products in Development***

## **Oncolytic Monoclonal Antibodies**

- Oncology Pipeline
- Novel mAbs
- mAb fragments
- mAb conjugates
- Bispecific T-cell engagers
- Tandabs

# ***Future Horizons***

## ***Products in Development***

### **RNAi: (RNA interference) based drugs**

- ✦ Nanoparticles
- ✦ Lipid-based nanoparticles
- ✦ Liposomes

oncology (angiogenesis), endothelial diseases

“Delivery Approaches for RNAi-Based Drugs” James Netterwald, Ph.D., Genetic Engineering News, Vol 29, No 11, June 1, 2009





# ***Future Horizons Products in Development***

## **RNAi: (RNA interference) based drugs**

- ✦ “Fusion proteins” (peptide transduction domain)  
***personalized oncology therapies***
- ✦ Conjugated (aptimer-siRNAs)  
HIV-1 (bound to HIV-1 envelope protein)
- ✦ shRNA (short hairpin RNA)  
genetic conditions

“Delivery Approaches for RNAi-Based Drugs” James Netterwald, Ph.D., Genetic Engineering News, Vol 29, No 11, June 1, 2009

# ***Product Delivery***

-  **Material and manipulation for product administration**
-  **Hazard potential**
-  **Special needs in adverse conditions.**
-  **Alternate Health Care delivery.**

# ***Product Delivery***

-  **Initially designed for delivery in a clinical setting.**
-  **Special needs in adverse conditions.**
-  **Alternate Health Care delivery.**

# ***Conventional Reconstitution of a Lyophilized Product***



from “Practical Aseptic Processing: Fill and Finish”

# ***Clinical Delivery***

## **Material Cost**

**Product and diluent**

## **Transfer/administration**

**Syringe and two needles**

## **Effort**

**Diluent addition**

**Reconstitution**

**Solution withdraw**

# ***Conventional Clinical Delivery***

## **Multiple steps in product administration**

**1-Draw diluent**

**2-Extrude diluent into product vial**

**3-Swirl or shake to dissolve**

**4-Draw dosage volume from vial**

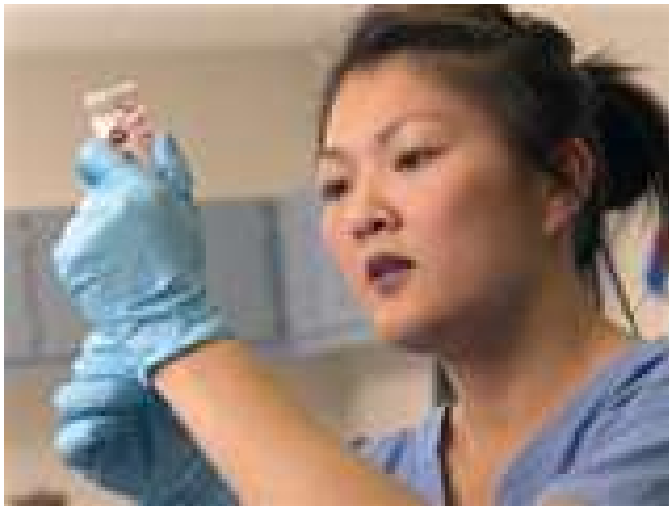
**5-Change needle**

**6-Administer product to patient**

# ***Clinical Setting Delivery***

## ***Conventional administration***

### **Physicians office**



### **Hospital Setting**

# ***Product Delivery***

-  **Initially designed for delivery in a clinical setting.**
-  **Special needs in adverse conditions.**
-  **Alternate Health Care delivery.**

# ***Product Delivery***

## **Critical care products**

✦ Dantrium IV

P&G, Top 800

✦ Actavase (TPA)

Genentech/Roche



# ***Product Delivery***

-  **Initially designed for delivery in a clinical setting.**
-  **Special needs in adverse conditions.**
-  **Alternate Health Care delivery.**

# ***Alternate Health Care Delivery***



## **Chronic conditions:**

hemophilia, MS, Crohn's



## **Post-operative care:**




Organ transplant, infections.



## **Targeted treatments:**

Oncology, congestive heart failure, parenteral nutrition.

# ***Alternate Health Care Delivery***




-  **Condition does not require hospitalization.**
-  **Requires skilled practitioner's medication administration.**
-  **An inherently local service provider.**

“Traveling the Home Infusion Route for Specialty Pharmaceutical Distribution”  
Pharmaceutical Commerce, Jeff Siegel, September 2007




# ***Alternate Health Care Delivery***

-  **Hospital Outpatient Centers.**
-  **Home-infusion Services.**
-  **Alternative Infusion Centers (AICs).**

# ***Alternate Health Care Delivery***

-  **“High touch” specialty therapies.**
-  **Requires skilled practitioner for administration.**
-  **An inherently local service provider.**

# ***Considerations in Product Delivery***

-  **Patient Compliance**
-  **Hazard potential**  
**“Needle stick”**
-  **Handling hazardous products**

# ***Growth of Novel Product Delivery***

## **Prefilled syringe to replace syringe and vial.**

- Current market of prefilled syringes of 2 to 2.5 billion units per year.**
- Greater than 10% growth increase each year.**

Visiongain “Prefilled Syringes 2009”, 01-02 October 2009, London UK

# ***Convenient Reconstitution for a Lyophilized Product***



# ***Convenient Reconstitution for a Lyophilized Product***



from “Practical Aseptic Processing: Fill and Finish”

# ***Future Product Delivery***



**Prefilled pen device to replace syringe and vial.**

**Byetta (exenatide) (Lilly/Amylin)**



# ***Future Product Delivery***

## **Needle-Free Injection Therapy (Bioject)**

-  International AIDS Vaccine Initiative: Packaging for ADVAX DNA based vaccine.**

# ***Future Product Delivery***

## **◆ Implantable drug delivery device (MicroCHIPS)**






**Daily deliver of PTH(134) for osteoporosis  
Received 2008 AAPS Drug Delivery  
Technology Award**

“The New and Improved You”, Inc., October 2009,

# ***Future Product Delivery***

## **Competing factors**

-  **Infusers for High Volume Drugs**
-  **Microneedles**
-  **Needle Free Devices**
-  **Direct Solid Injection (no needle)**

Injectable Drug Delivery – How Far Have We Come and Where are We Going?,  
Mathias Romacker, Pharmaceutical Outsourcing, Vol 10 #4 July/August 2009,

# ***Current Development Products***

**Tufts University analysis indicated more than one-third of pipeline products are via invasive administration.**

Injectable Drug Delivery – How Far Have We Come and Where are We Going?,  
Mathias Romacker, Pharmaceutical Outsourcing, Vol 10 #4 July/August 2009.

# Summary

- ✦ **The science and technology has grown to be more widely applied for high value health care products.**

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- ✦ **The science and technology has grown to be more widely applied for high value health care products.**
- ✦ **Our understanding of the scientific principles and application of improved methods in formulation and processing has led to more effective and efficient development and manufacturing.**
- ✦ **Continued investment in training and research is essential to meet the future demands.**

# ***The Future of Development***

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- **Pharmacology and clinical requirements dictate product administration.**
- **Product administration influences delivery “system”.**
- **Delivery “system” guides product design.**
- **Product design directs manufacturing needs.**
- **Manufacturing needs mandate new development objectives.**

**Onward to the Future**