



# OVERVIEW OF BIOPHARMA INDUSTRY

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# WORLD MARKET

SOURCE: POPULATION REFERENCE BUREAU, 2004 POPULATION

## FIGURES

○ World	6 billion, 396 million
○ U.S.	293.6 million
○ Europe	728 million
○ Japan	128 million
○ Canada	31.9 million
○ Australia/New Zealand/Pacific	33 million
○ Asia	3 billion, 875 million
○ Africa	885 million
○ South America	365 million

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# 2009 WORLD PHARMACEUTICAL MARKET

SOURCE: IMS HEALTH

- World Pharmaceutical Market \$ 808 billion
- North America \$ 322 billion (up 5.5%)
- Europe \$ 248 billion (up 4.8%)
- Africa/Asia/Australasia \$ 103 billion (up 15.9%)
- Japan \$ 90 billion (up 7.6%)
- Latin America \$ 46 billion (up 10.6%)

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# TOP PHARMACEUTICAL MARKETS

SOURCE: IMS HEALTH WORLD REVIEW, 1997

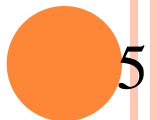
- U.S.
- Japan
- Germany
- France
- Italy
- U.K.
- Brazil
- Spain
- China
- Canada

# WORLDWIDE PHARMACEUTICAL COMPANIES 2009 (PHARMACEUTICAL SALES \$ BILLIONS)

SOURCE: IMS HEALTH

○ Pfizer	\$57
○ Merck	\$39
○ Novartis	\$38
○ Sanofi-Aventis	\$36
○ Glaxo Smithkline	\$35
○ Astrazeneca	\$34
○ Roche	\$33
○ Johnson & Johnson	\$27
○ Eli Lilly	\$20
○ Abbott	\$20
○ Teva	\$16
○ Bayer	\$16

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# SOME U.S. BIOTECH COMPANIES (\$ BILLIONS)

*2009 REVENUES SOURCE: VARIOUS INTERNET SOURCES*

○ Amgen Inc.	\$14.6
○ Genentech Inc.	\$9.5
○ Gilead Sciences Inc.	\$5.9
○ Genzyme Corp.	\$4.5
○ Biogen Idec Inc.	\$4.4
○ Cephalon, Inc.	\$2.2
○ MedImmune Inc.	\$2.0
○ Celgene.	\$0.8
○ Amylin Pharmaceuticals	\$0.8

# TOP 10 PRESCRIPTION DRUGS IN 2004 (\$ BILLIONS US SALES)

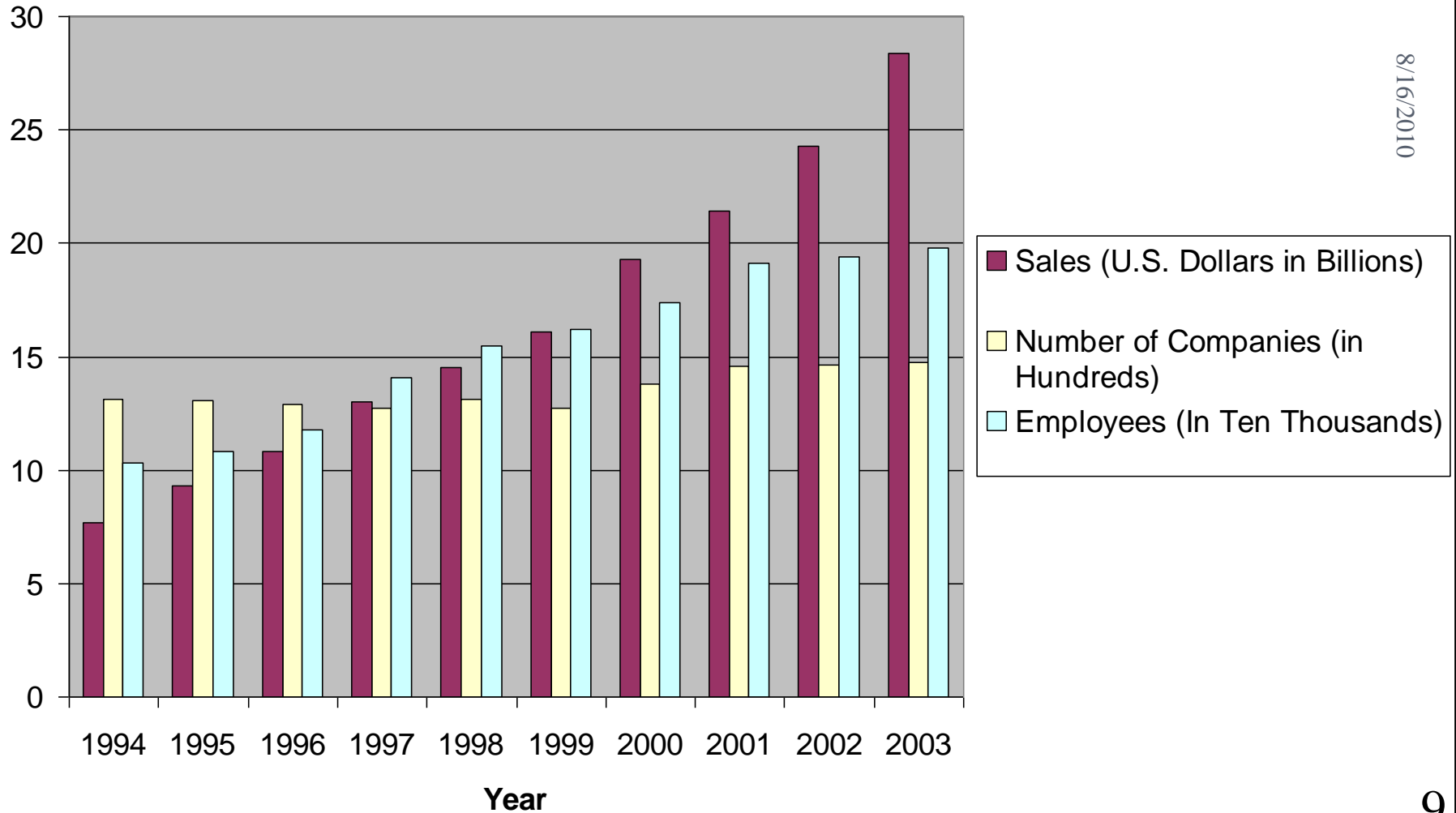
*SOURCE: IMS HEALTH*

1.	Lipitor	13.3
2.	Plavix	9.1
3.	Nexium	8.2
4.	Seretide	8.1
5.	Seroquel	6.0
6.	Enbrel	5.9
7.	Remicade	5.5
8.	Crestor	5.4
9.	Zyprexa	5.4
10.	Humira	5.0

# MAJOR BIOTECH DRUGS ON MARKET ESTIMATED 2009 SALES - \$BILLION (SOURCE: VARIOUS)

1.	Epogen/Aranesp (Amgen)	6.1
2.	Avastin (Genentech)	5.7
3.	Rituxan (Genentech/ Biogen-Idec)	5.6
4.	Humira (Abbott)	5.0
5.	Remicade (Johnson & Johnson/ Schering)	4.3
6.	Neupogen/Neulasta (Amgen)	4.6
7.	Enbrel (Amgen/Wyeth)	3.5
8.	Humulin/Humalog (Genentech/Eli Lilly)	3.0
9.	Avonex (Biogen-Idec)	2.3
10.	Procrit (Ortho/ Amgen)	2.2
11.	Recombinate/Advate (Baxter)	2.1

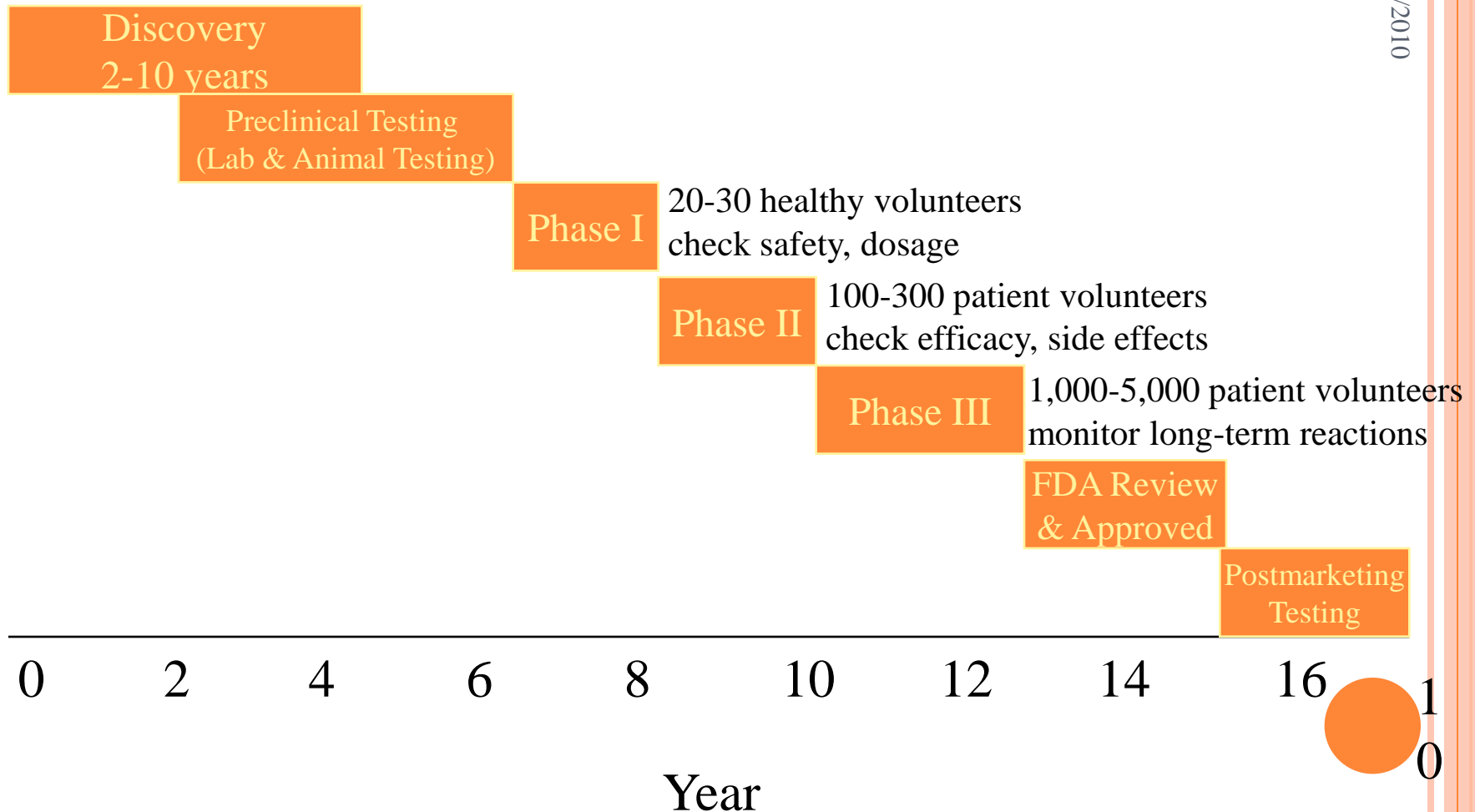
## U.S. Biotech Industry Statistics: 1994-2003



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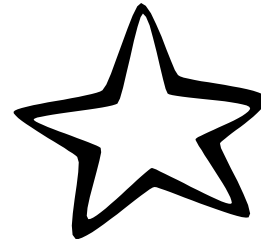
# BIOTECH DRUG DISCOVERY PROCESS

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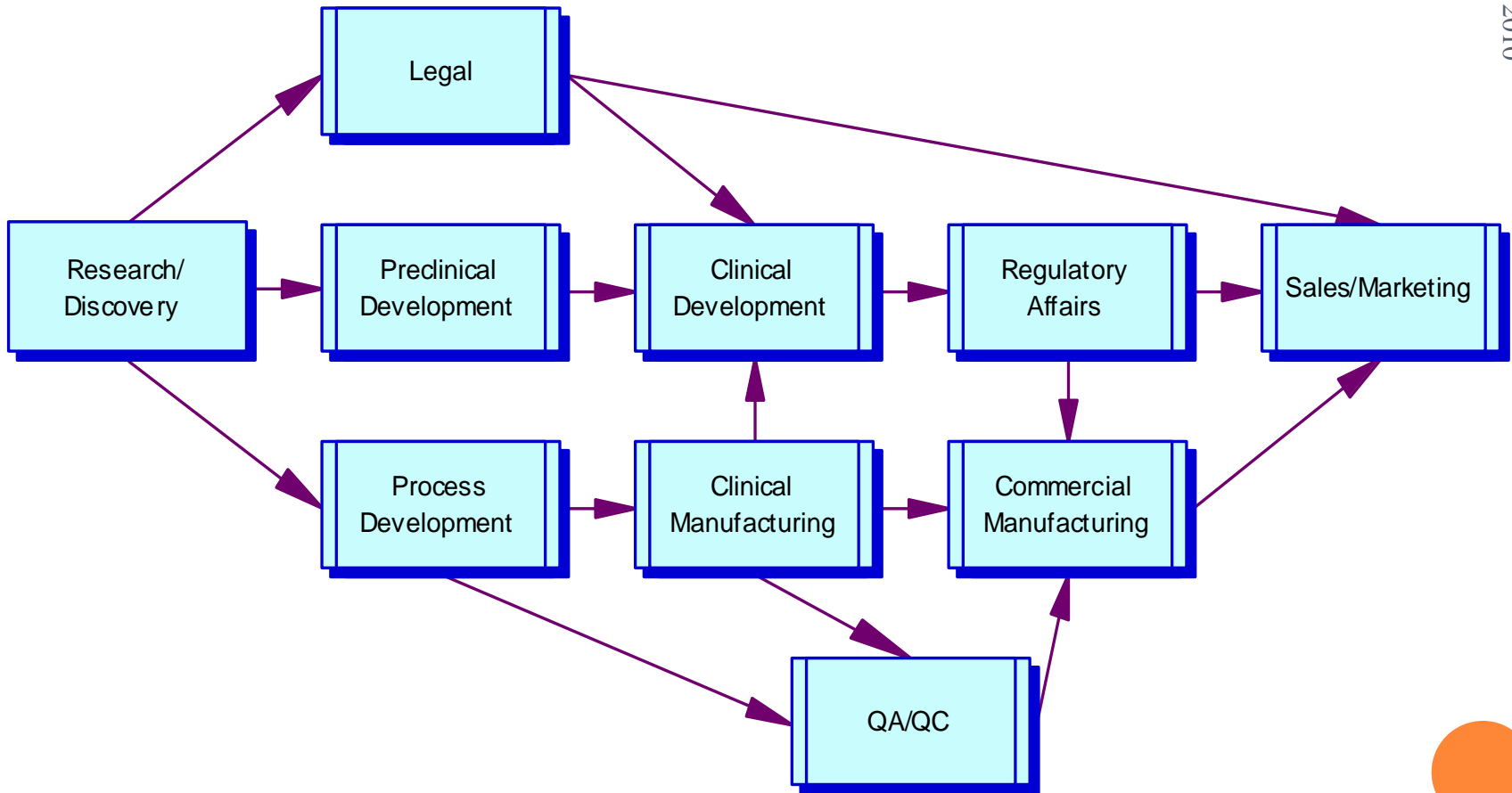


# Success Rates

- 5,000-10,000 compounds screened
- 250 enter preclinical testing
- 5 enter clinical testing
- 1 approved by FDA



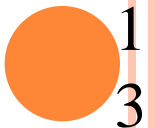
# Some Departments Involved in Product Development



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# NOW LET US FOCUS ON MANUFACTURING OF BIOLOGICS...

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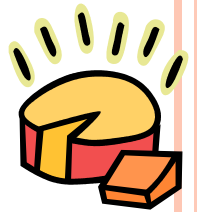
# WHAT IS BIO-MANUFACTURING?

- Use of biological agents (bacteria, mammalian cells, enzymes, viruses etc.) to produce commercially useful products
  - e.g. antibiotics, ethanol, detergents, cheese, AND genetically engineered products
- Focus of this course is on manufacturing of genetically engineered products for human therapeutic use
- Typically, gene of the product of interest is inserted in bacteria or mammalian cells and the cells grown to produce the product

# A BRIEF HISTORY



- *7,000-5,000 B.C.* - Earliest beer-making by Sumerians and Babylonians
- *4,000 B.C.* - Egyptians using yeast to make bread
- *900 A.D. or earlier* - Soy sauce preparation by Japanese
- Many cultures use bacterial cells to make cheeses, yogurts, fermented milk
- Antibiotics produced by fungi and bacteria since the 1940s
- Modern Biotech industry started in the late 1970s after the advent of genetic engineering techniques



# Drugs and Biologics

- Drugs and Biologics are different due to:
  - Product
  - Source
  - Process

# Product Differences

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- Drug products are typically small, easily characterized molecules made from chemical processes.  
Ex: Penicillin (MW = 346), Ibuprofen (MW = 106.28)
- Biologic products are typically large, complex molecules or proteins, made from complex or heterogeneous sources. They require complicated purification processes.  
Ex: Vaccines, Factor VIII, Human Growth Hormone (MW = 22,125)
- Biologics suffer from many types of modification that may not always be detectable.

# Source Differences

- Drugs are made by chemical synthesis and can be made in high yield and purity.
- Biologics are derived from complex biological sources such as blood, tissue, cells, or cultured eggs.
- These sources are susceptible to contamination and may be heterogeneous in composition.
- Numerous problems have occurred with source materials used to make biologics.

# Differences in Manufacturing Processes

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## Drug

- Chemical Synthesis
- Extraction
- Purification
- Formulation
- Filling/Lyophilization/Packaging

## Biotech

- Fermentation or Cell Culture
- Cell Separation/Product Recovery
- Bulk Separation/Extraction
- Purification
- Formulation
- Filling/Lyophilization/Packaging

# CHARACTERISTICS OF BIOLOGICAL PRODUCTS

- Produced by prolonged aseptic processing
- Starting materials (bacteria, animal cells etc.) are ill defined, variable, unstable, and potentially contaminated
- Biological processes are variable in outcome
- Process conditions conducive to proliferation of contaminants – and inactivation may not be feasible

# CHARACTERISTICS OF BIOLOGICAL PRODUCTS....

- Purification steps must also be relied upon to remove viable contaminants
- Assays designed to detect low level contamination are relatively insensitive
- No single assay can assess quality of the product – need judgment based on cumulative data
- No reliable means of predicting product stability

# RISKS INVOLVED WITH BIOLOGICAL PRODUCTS

- Instability, variability, and contamination of starting material
- Variability of the cultivation process
- Inadequate purity and variability of potency of the product
- Potential for product to be contaminated with pathogenic viruses/ oncogenic DNA/extraneous agents
- Inability of in-vitro assays to confirm quality of final product – and insensitivity of bioassays

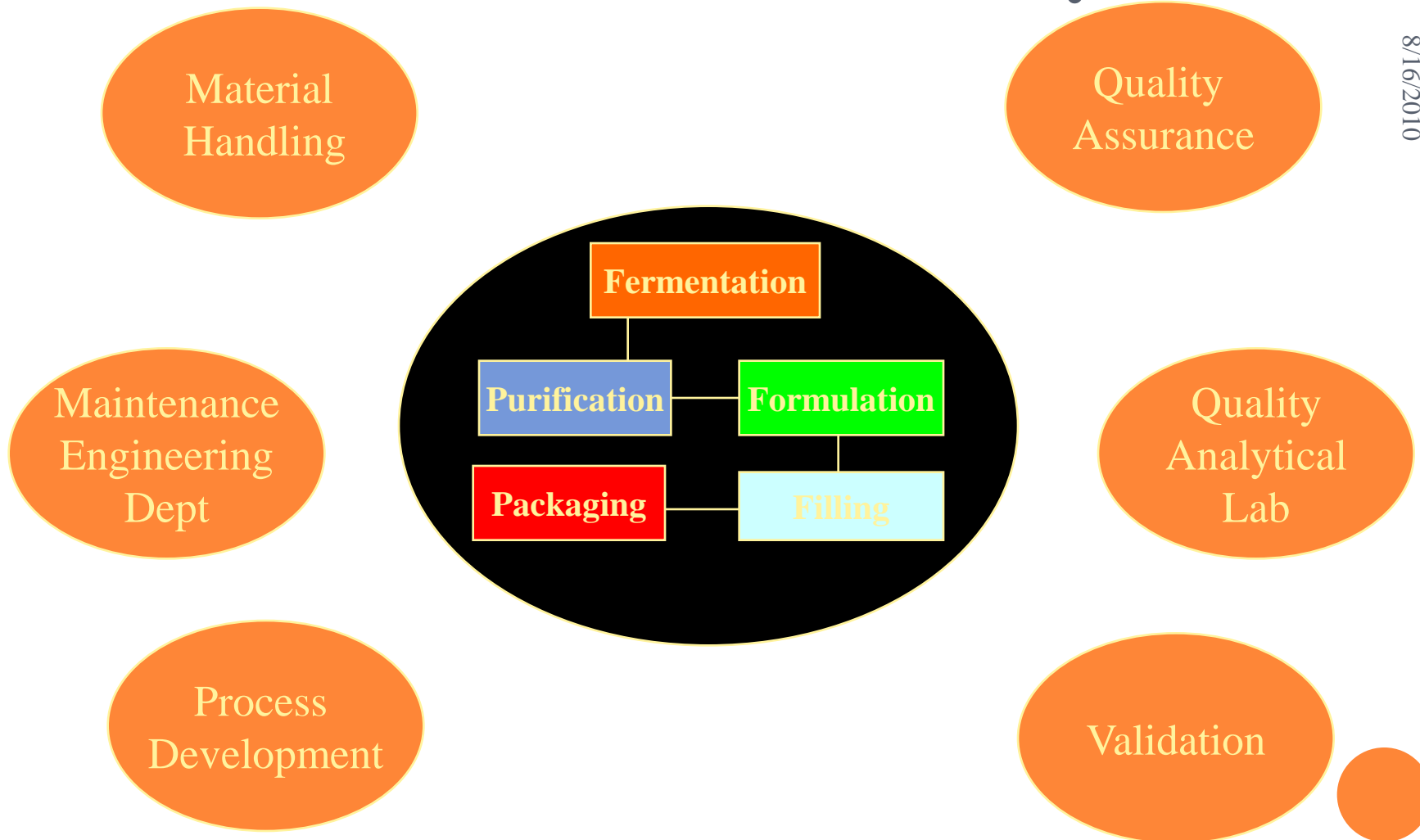
# THE PROCESS DEFINES THE PRODUCT

- Minimize biological variation
- Control contamination

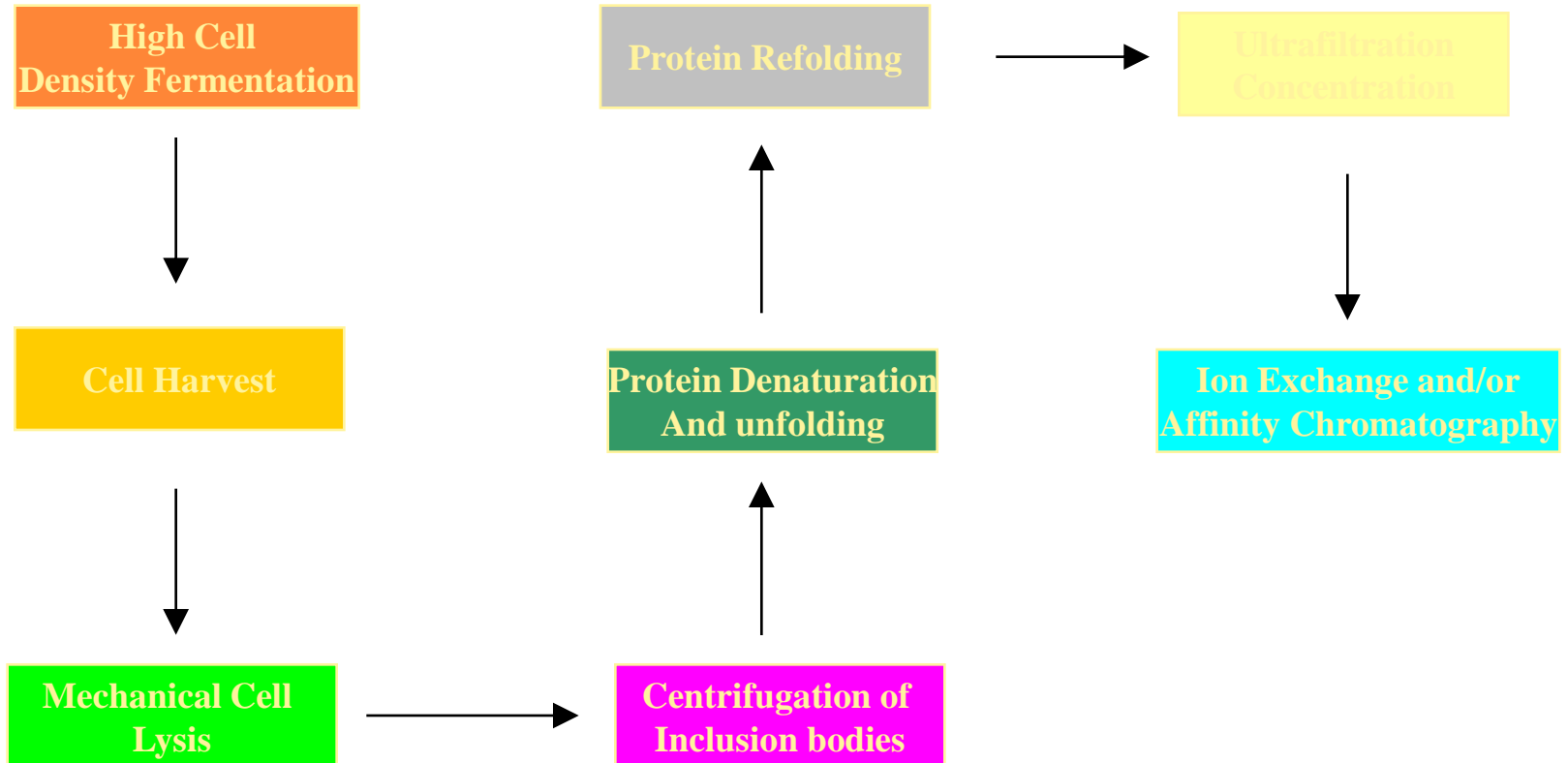
# BIOPROCESSING HAS SEVERAL QUALITY CONCERNS WITH RESPECT TO:

- Starting materials
- Fermentation/Cell Culture
- Purification
- Virus removal
- Cleaning validation

# OVERVIEW OF A BIO-MANUFACTURING PROCESS AND PARTNERS IN QUALITY



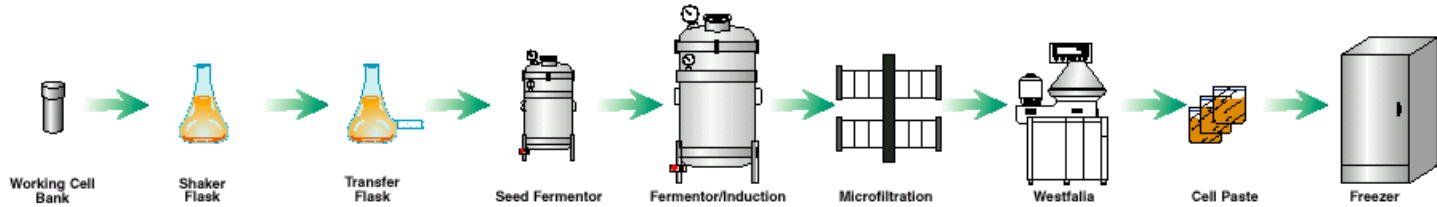
# BACTERIAL RECOMBINANT PROTEIN PROCESS FLOWSHEET



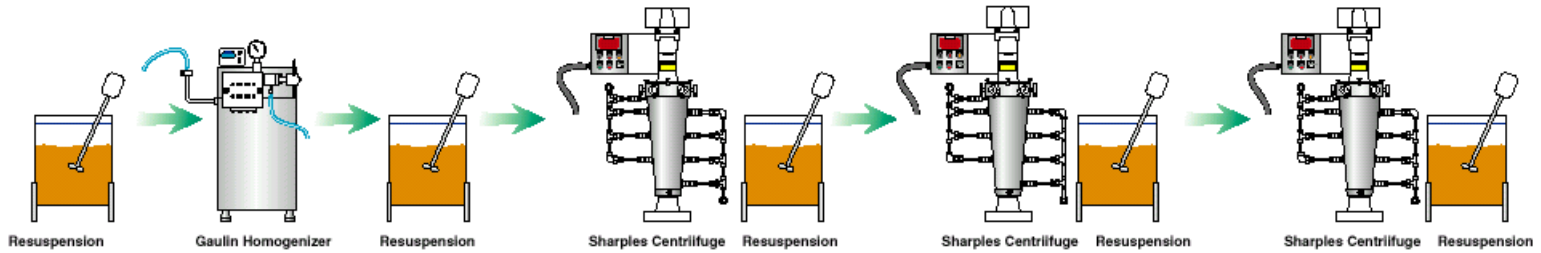
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# TYPICAL BACTERIAL PROCESS EQUIPMENT

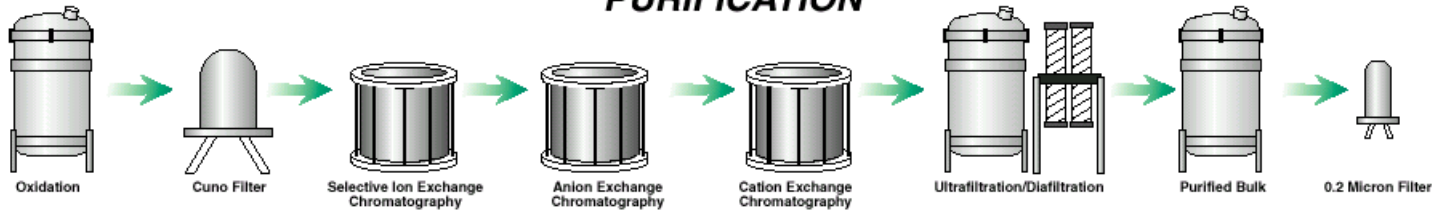
## FERMENTATION



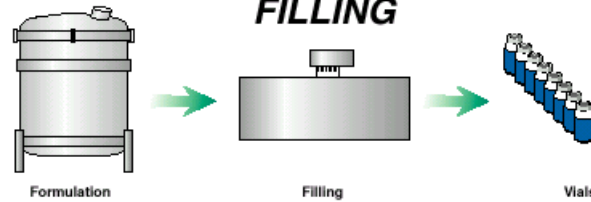
## RECOVERY



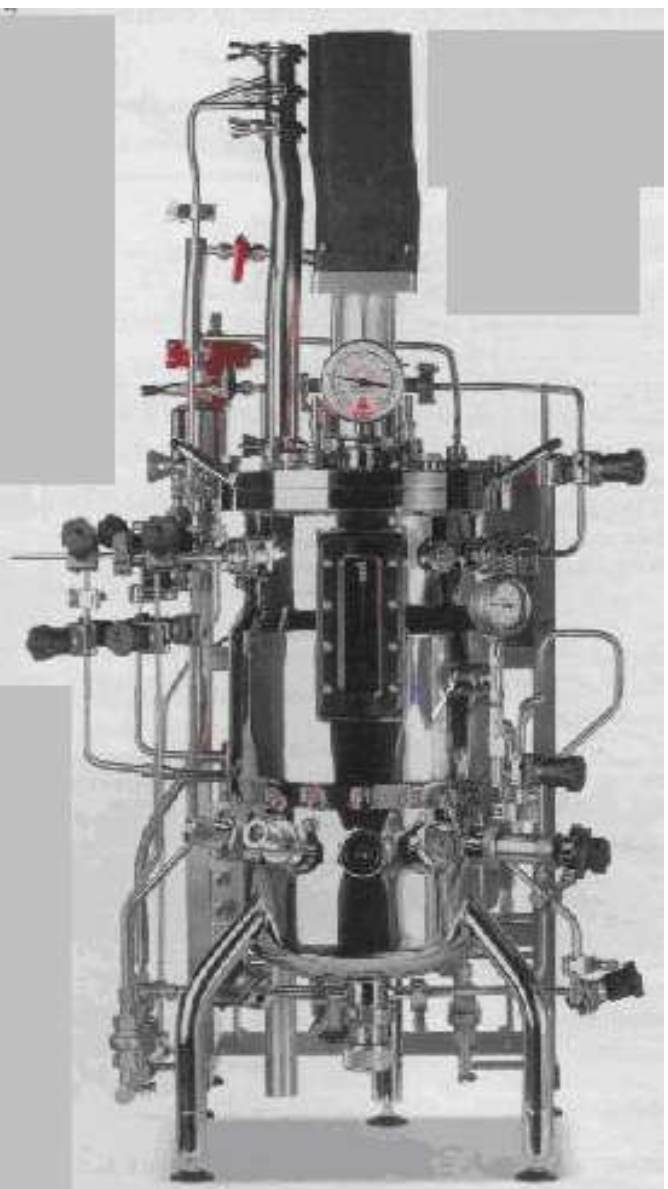
## PURIFICATION



## FILLING



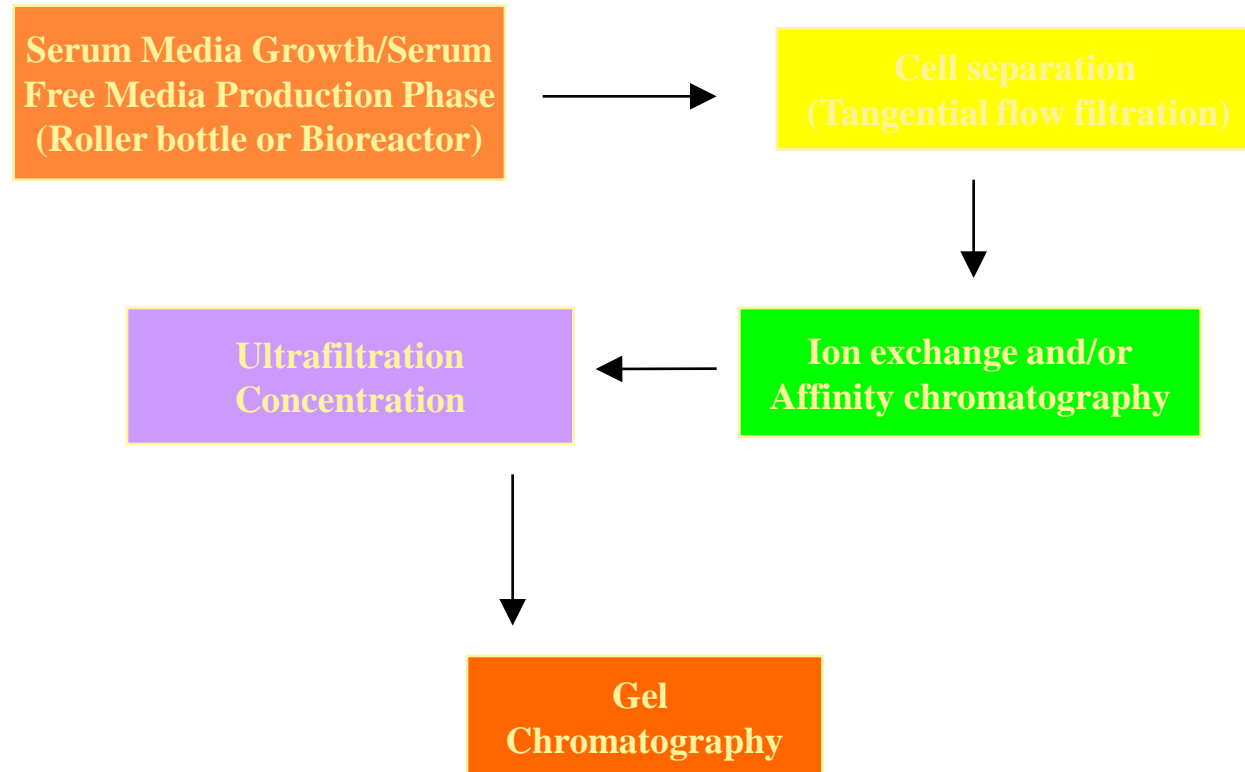
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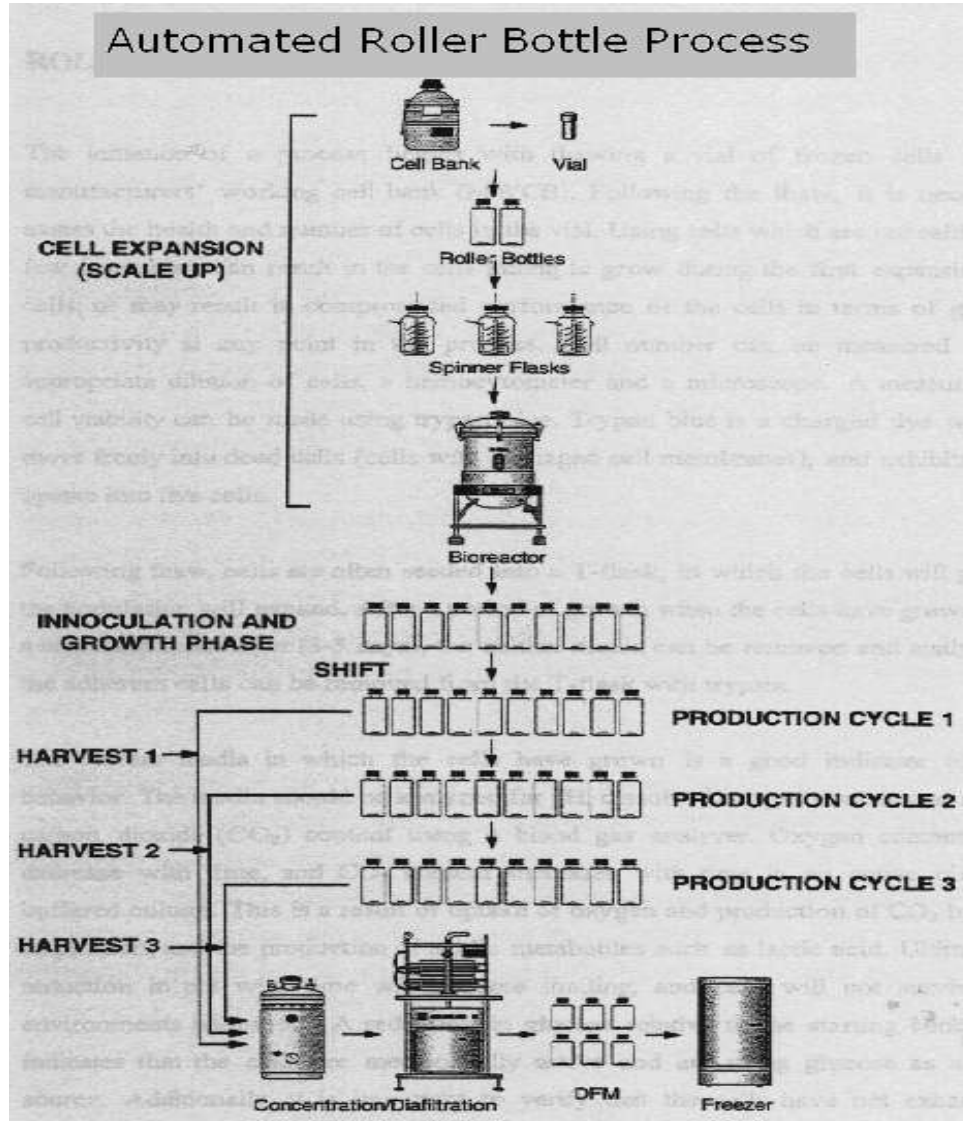
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# MAMMALIAN RECOMBINANT PROTEIN PROCESS FLOWSHEET

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# EQUIPMENT



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# TYPICAL FINAL FORMULATION STEPS

- Ultrafiltration concentration and/or diafiltration into final dosage formulation media
- Sterile filtration
- Sterile liquid filling or
- Lyophilization and sterile powder filling

# EVOLUTION OF GOOD MANUFACTURING PRACTICES (GMPs)

- The Food and Drugs Act of 1906
  - primarily adulteration/misbranding
- The Federal Food, Drug, and Cosmetic Act of 1938
  - primarily safety
- The Drug Amendments of 1962 and 1975
- Current GMPs published 1978
- Updated and revised regulations – 1990s

# U.S. Regulations in a Nutshell

Source: S. Mendivil, Amgen

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- Preclinical testing and development, including animal toxicology testing, must be performed following good laboratory practices (GLPs) (21 CFR 58) and IND regulations (21 CFR 312).
- Human clinical trials must be conducted according to good clinical practices (GCPs) (21 CFR 50, 56, 58, 312).
- Drug, biologic, and medical devices (including clinical and commercial products) for humans and animals must be manufactured per current good manufacturing practices (CGMPs). (21 CFR 210/211 for drugs & biologics, 21 CFR 820 for devices, & 21 CFR 600 for human biologics.)



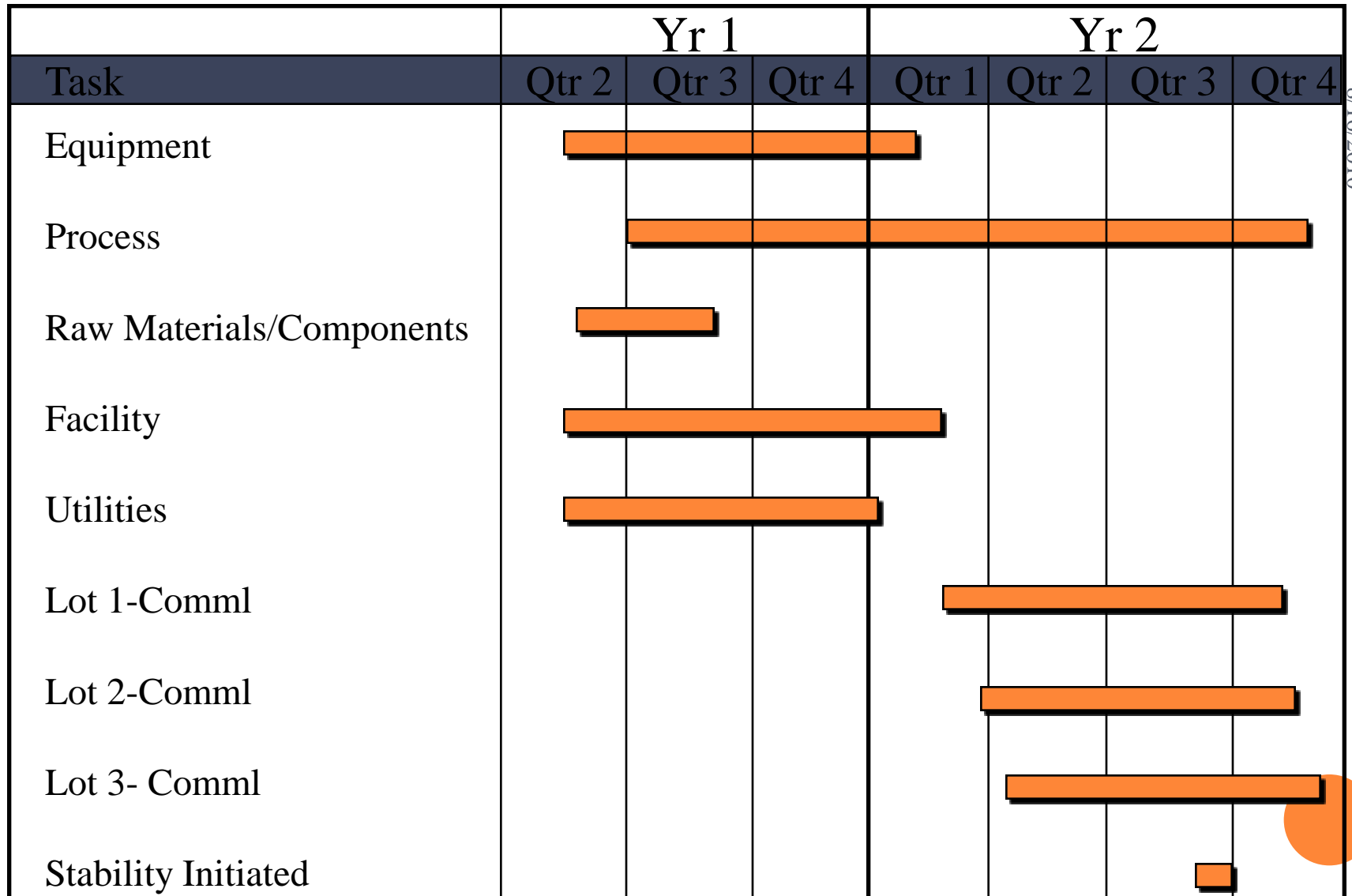
# GMP INTERPRETATION

- GMP requirements are interpreted through
  - “Guidelines” published by the FDA
  - “Points to Consider” published by the FDA
  - Numerous public and private meetings with FDA staff

# GMP PRINCIPLES

- Quality, safety, and effectiveness must be designed and built into the product
- Quality cannot be inspected or tested into a final product
- Each step in a manufacturing process must be controlled to ensure that the final product meets quality and design specifications

# Operations Timelines



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# FINAL THOUGHTS

- In the business of saving, extending and enhancing people's lives!
- Use of cutting edge technology to make state of the art products
- Responsible for handling liquid gold
- Responsible for people's lives!

QUESTIONS?

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