The Biotech Industry Past, Present, and Future

PMDA

February 15, 2007

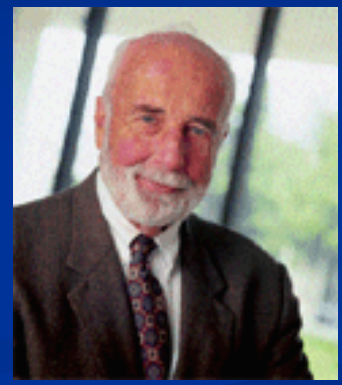
Rob Garnick
Sr. VP, Regulatory, Quality & Compliance
Genentech

The Birth of Biotech

- The Pioneers

Stanley Cohen
Stanford University

Bob Swanson &
Herb Boyer
Genentech



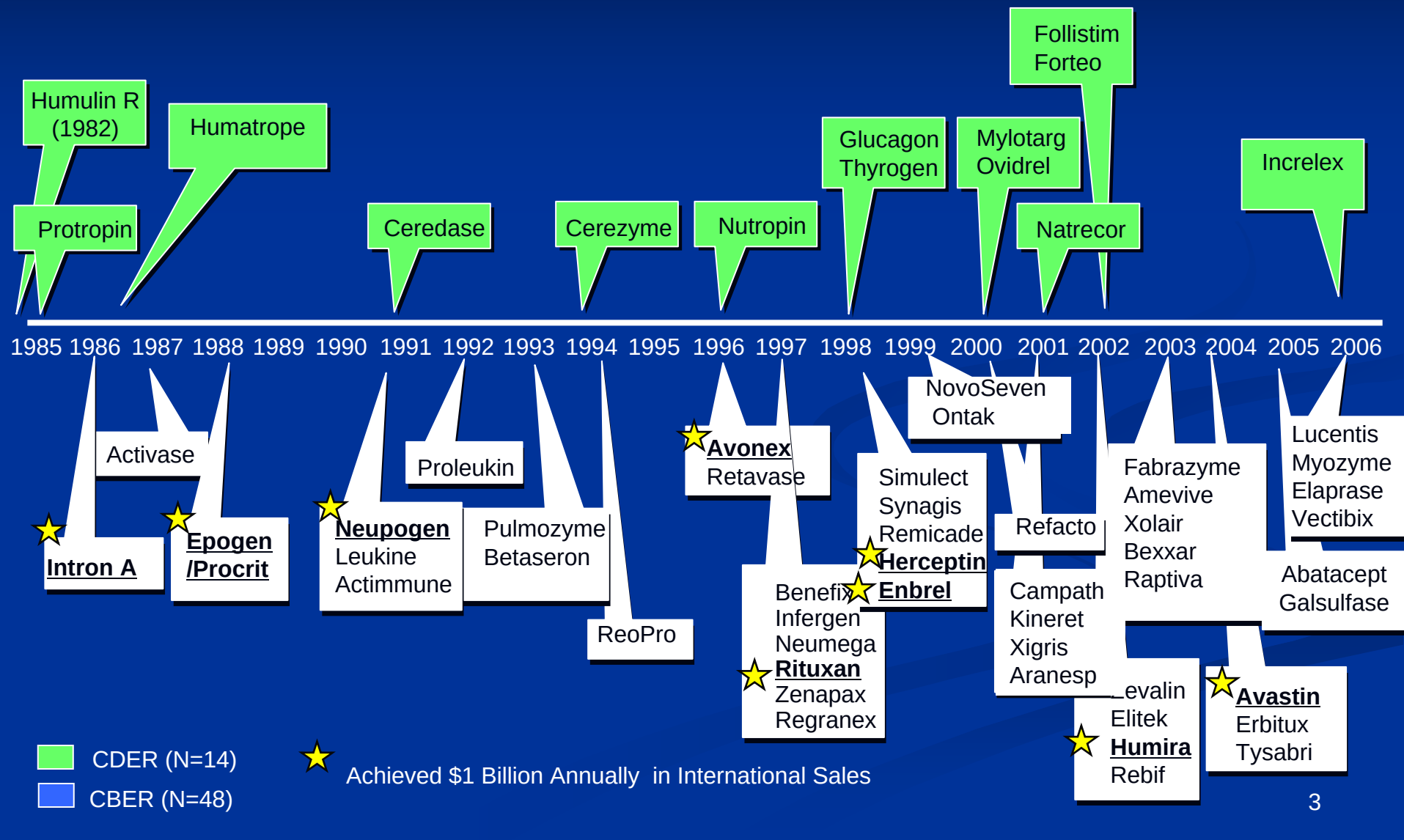
George Rathmann
Amgen CEO…

The Goal:

To develop unique microorganisms that are capable of producing products that will significantly better mankind.

Chronology of Key Biotech Product Approvals

NME's - 1982-2006



CDER (N=14)

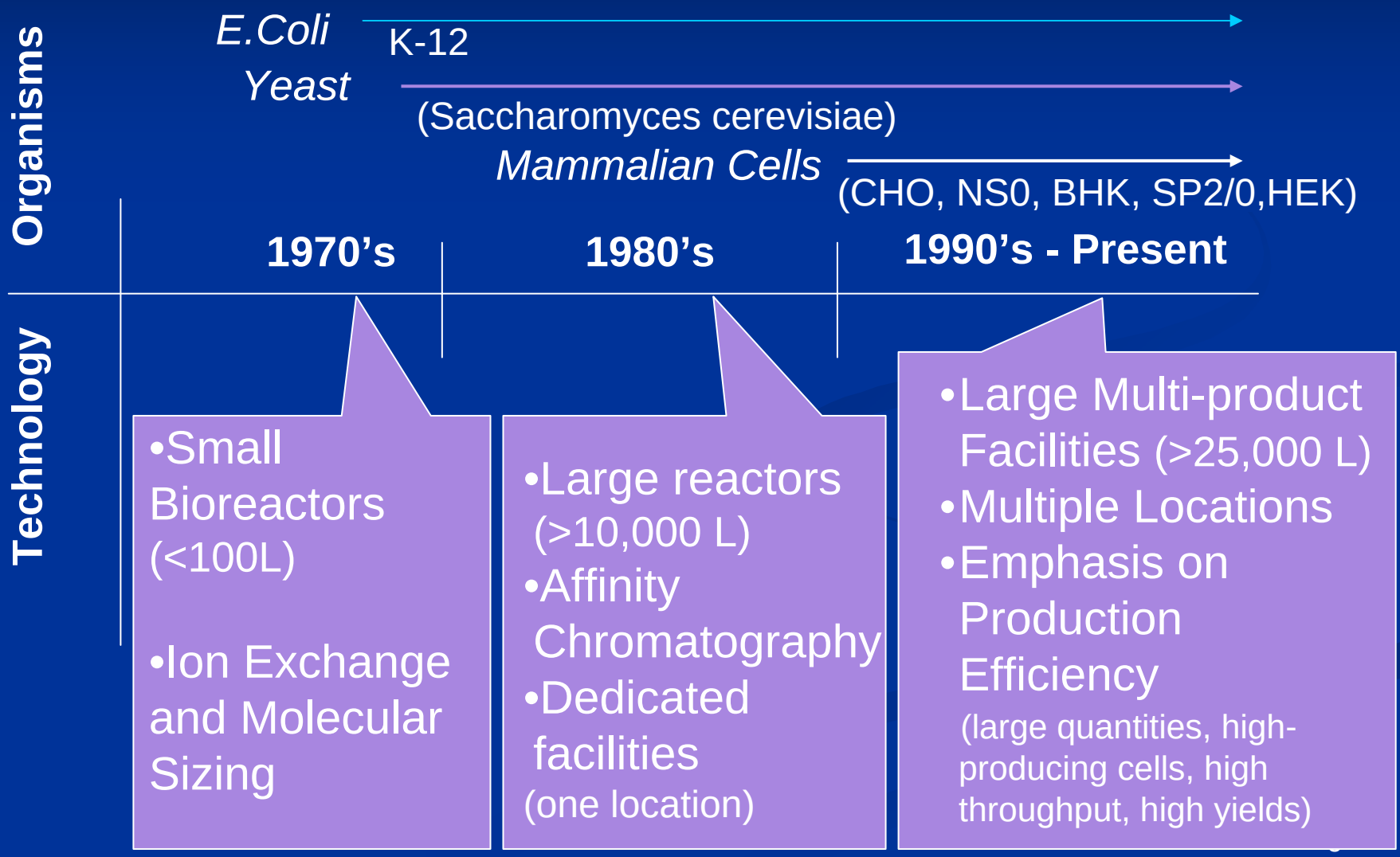
CBER (N=48)

Achieved $1 Billion Annually in International Sales

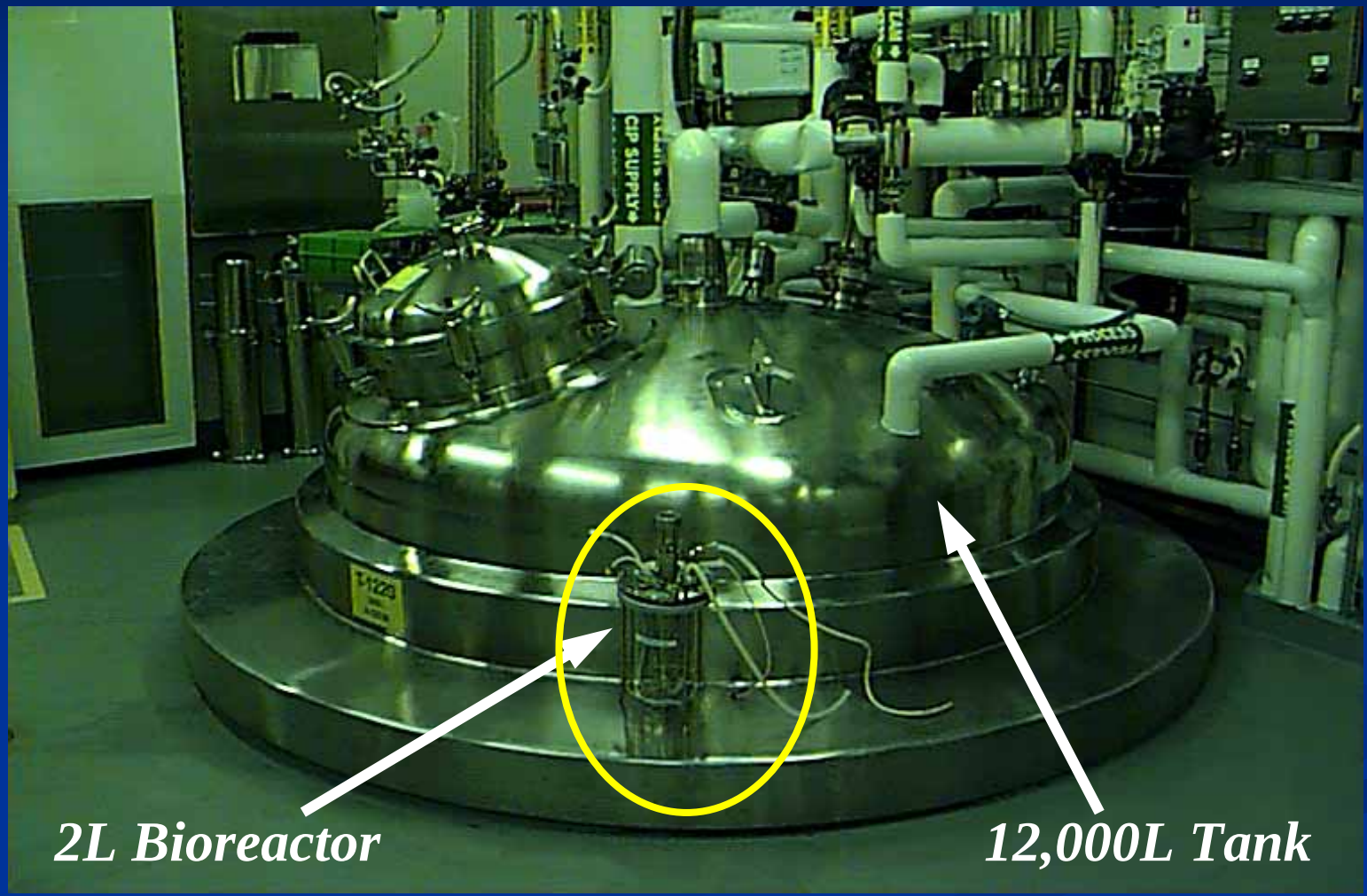
Biotech Products in Japan

- 8 of the top 100 products sold in Japan are from biotechnology with total sales in FY 2006 of 118 billion yen
  - Epoetin–alpha
  - Epoetin–beta
  - Lenograstim
  - Hyaluronate sodium
  - Infliximab
  - Rituximab
  - Filgrastim
  - trastuzumab

Evolution of Biotech Manufacturing



Cell Culture



1980's Capacity 2 kg 2000 Capacity 12,000 kg

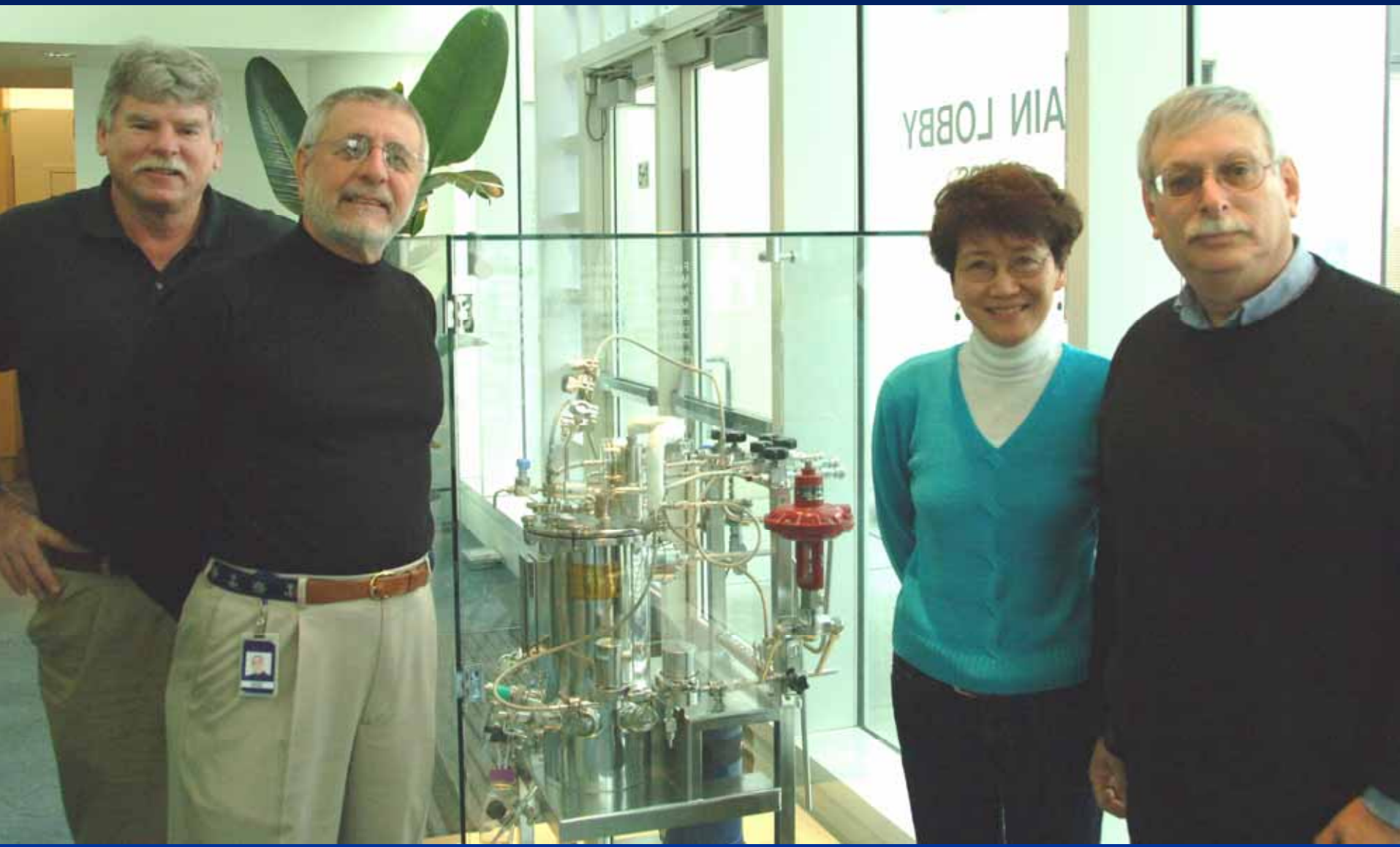
Today's Manufacturing Scale

Antibody-based biologics require:

- **Gram doses**
- **High concentration for subcutaneous use**
  >150 mgs/ml
- **Large scale mfg.**

"One Small Step for Biotechnology…"

In the Beginning…

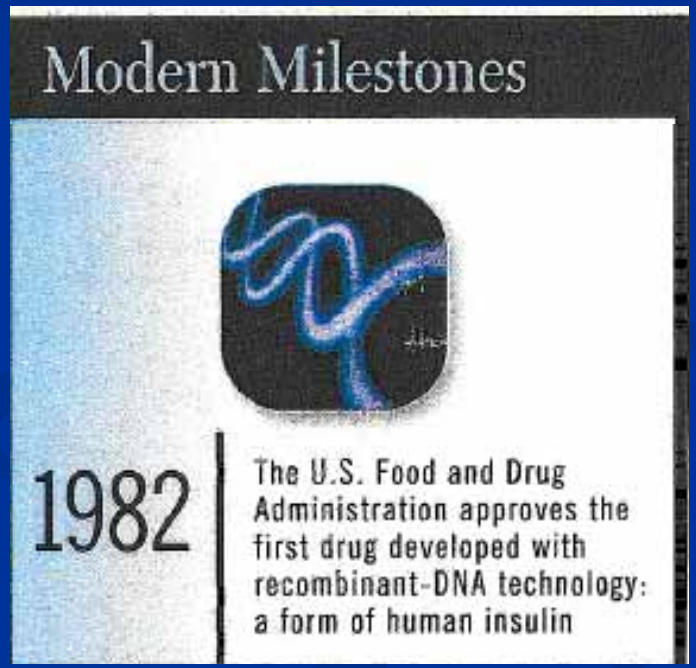


Today's Needs – Overcoming The Recovery Bottleneck…

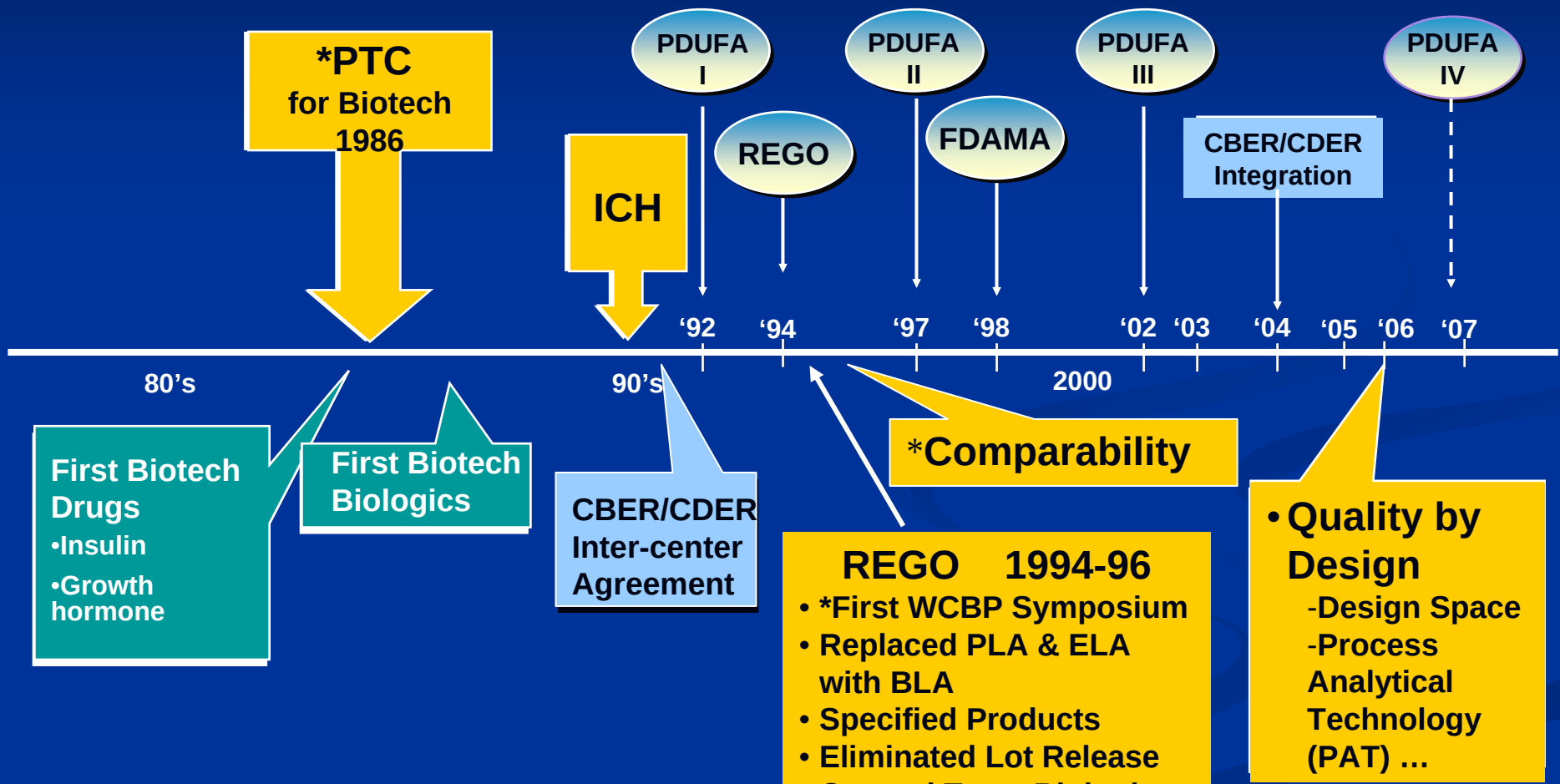
- Flexible and reconfigurable equipment easily scalable to changing needs
- Disposable technologies that avoid CIP and SIP infrastructure and associated validation requirements
- Increased use of controlled non-classified space and closed systems
- Reduce capital and operating costs
  - Reduced facility complexity
- Increased speed of facility licensure
  - Reduced regulatory burden

Regulatory Milestones

→



History of U.S. Biotech Regulation



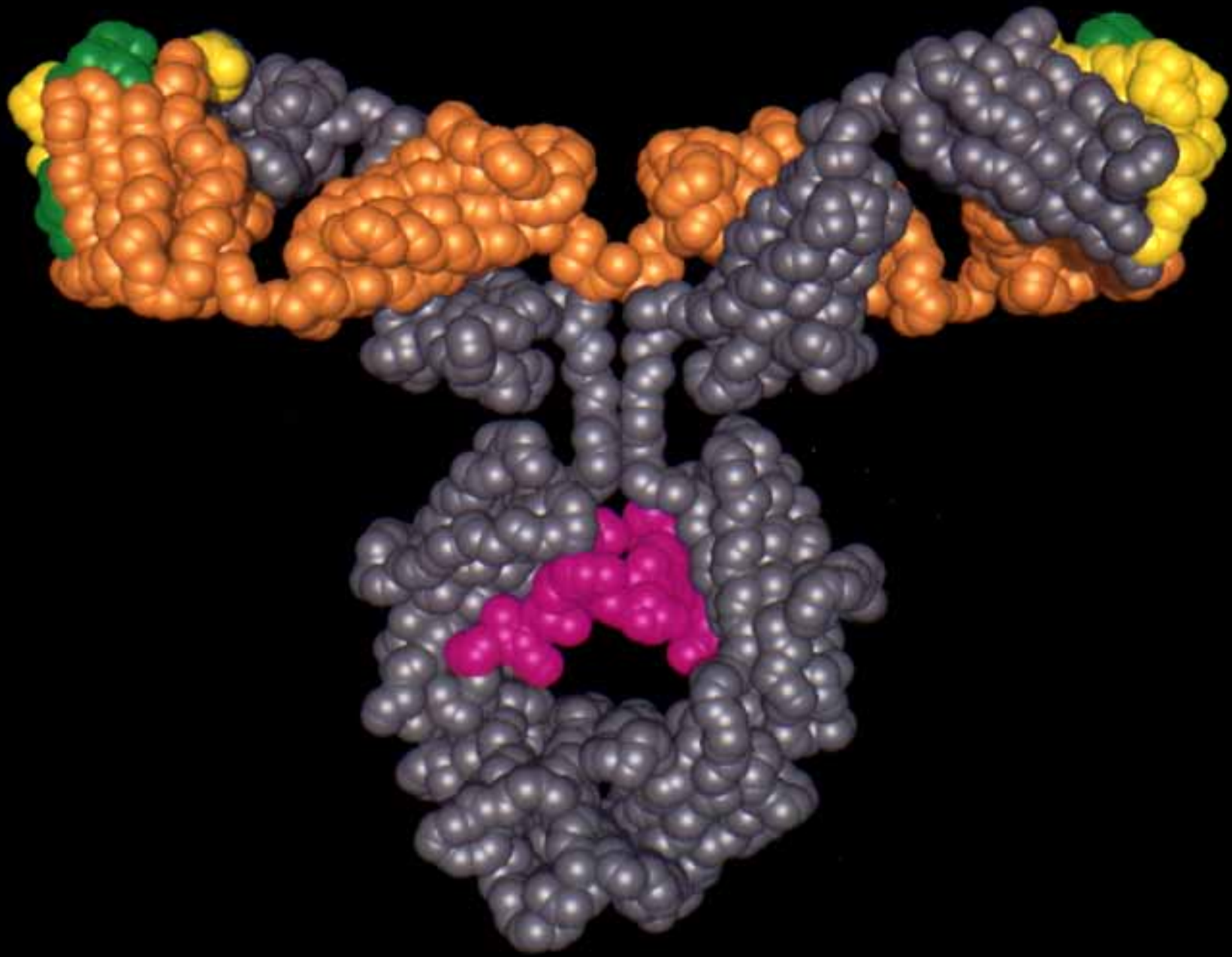

CLONE OR DIE
GAATTC
GENENTECH

Current Scientific Regulatory Concerns

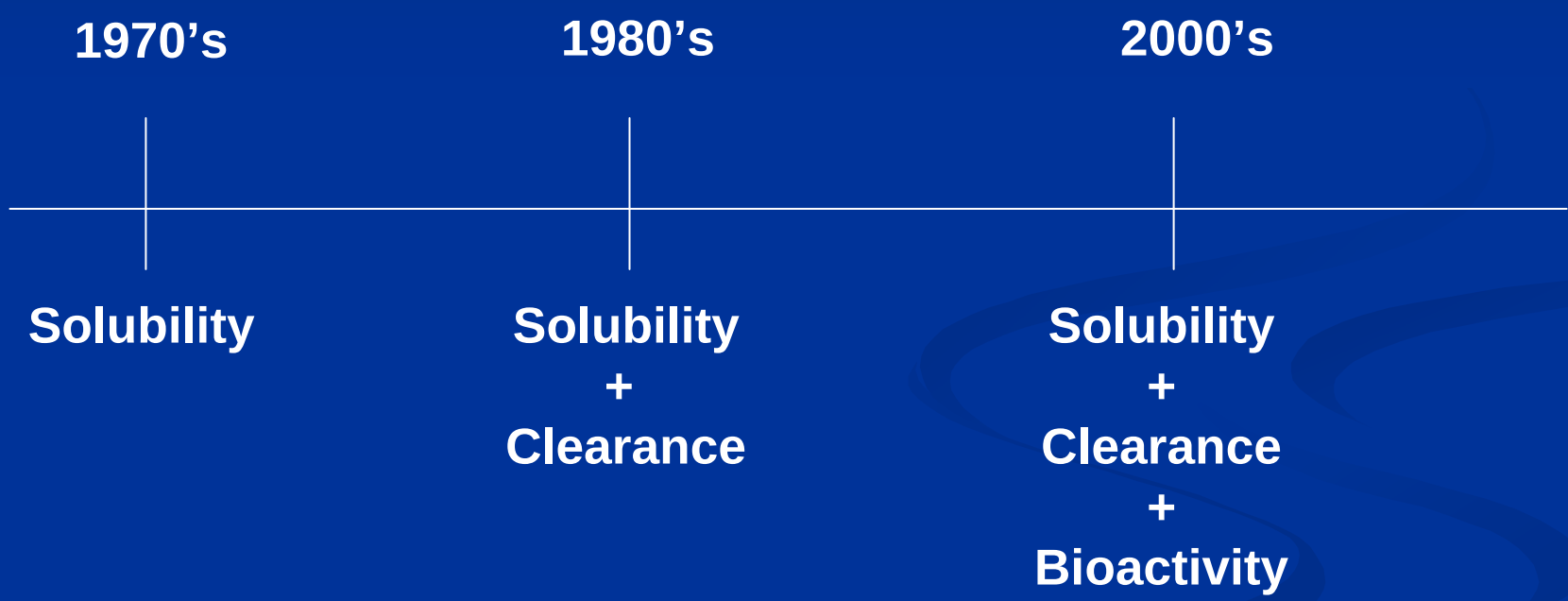
- DNA
- Genetic Stability
- Mutation
- Host Cell Proteins
- Endotoxins
- Intrinsic Virus
- **Extrinsic Virus**
- **Mycoplasma**
- **Aggregates** →

- **Glycosylation**
- **Immunogenicity**
- Deamidation
- Use of Immortalized Cell Lines
- Analytical Characterization of Proteins
- Reproducibility of Process
- **Stability**
- Product Specifications
- **Prions** →
- **Leachables / Extractables** →

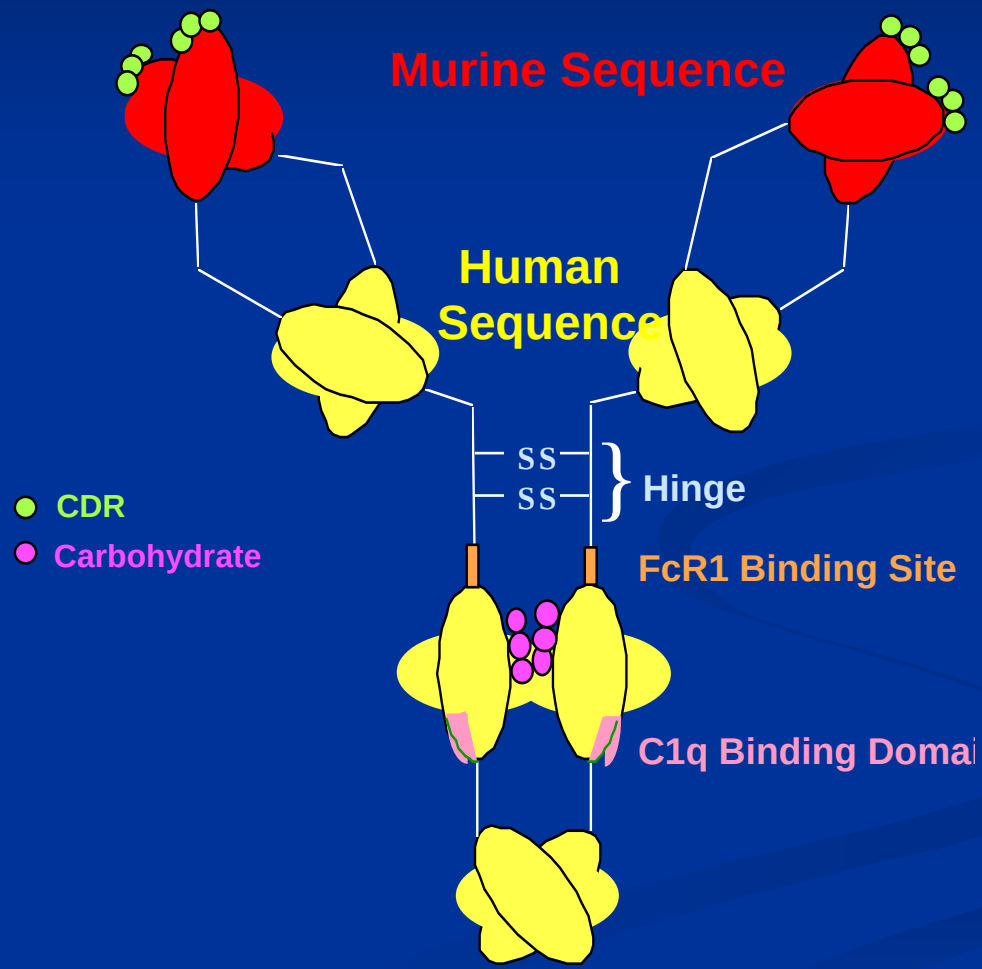
Message: Focus on what is still important.



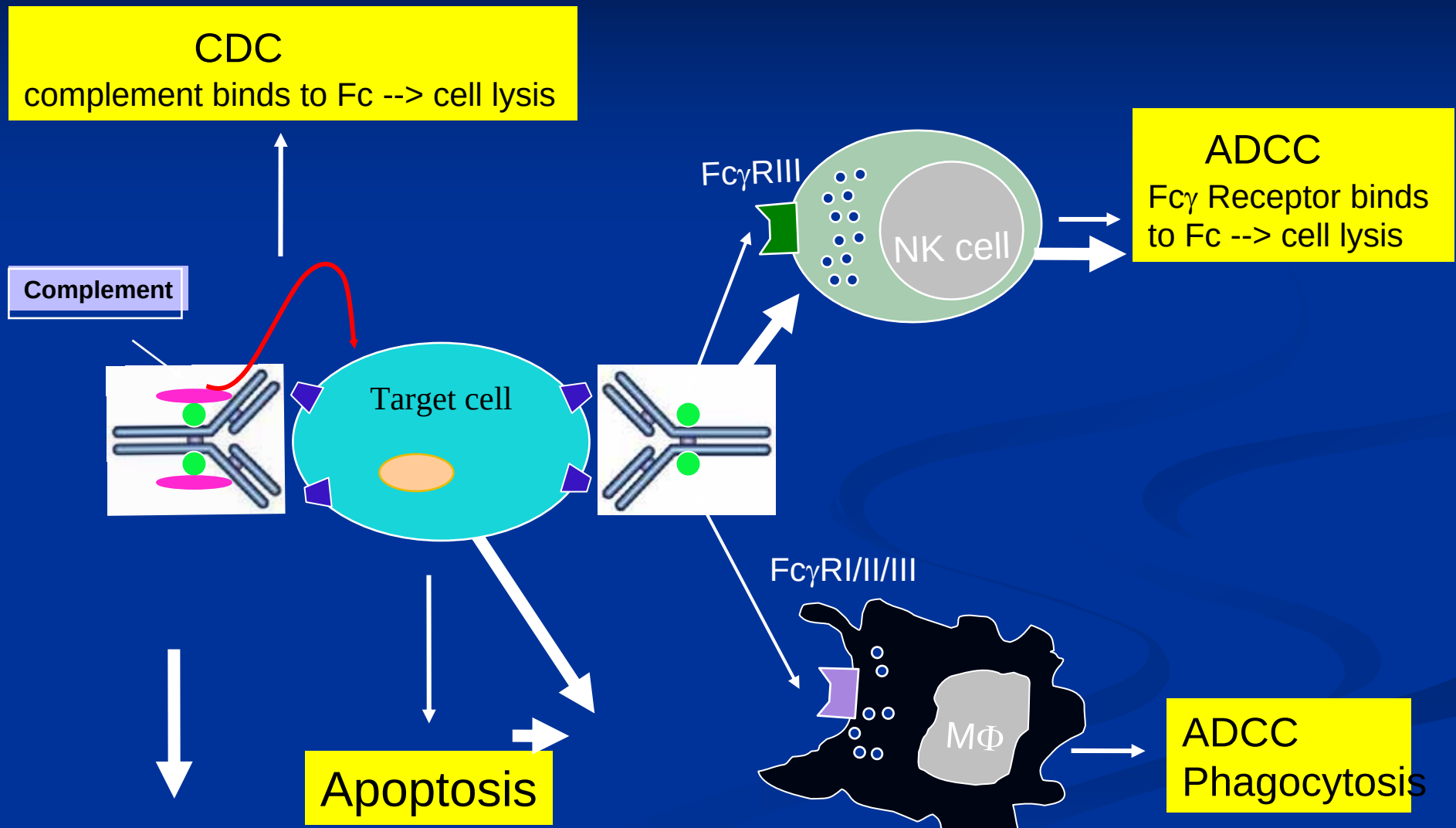
Glycosylation Then and Now



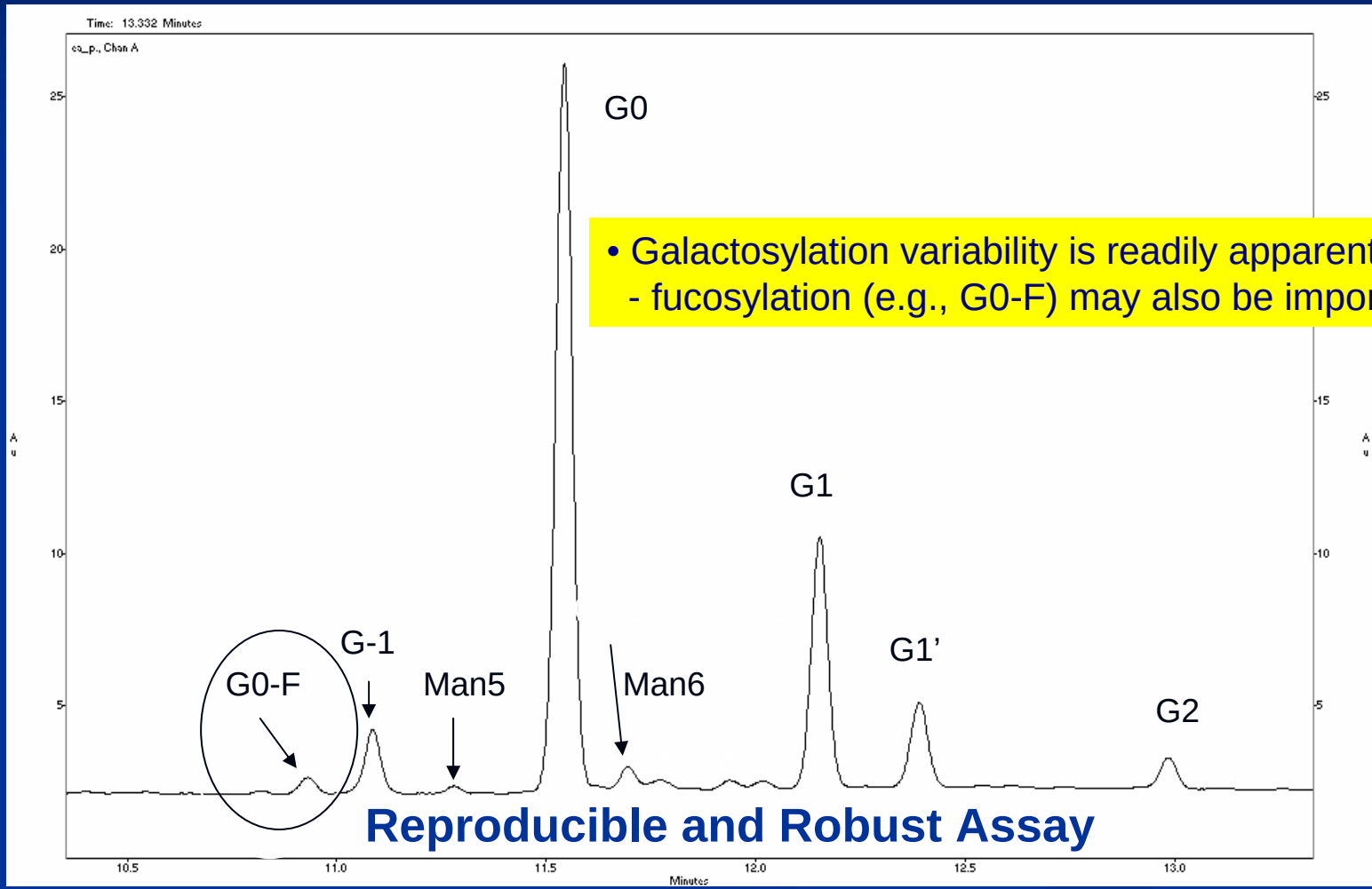
Rituxan: Antibody to the Human CD20 Antigen



Possible Mechanisms of Cell Killing



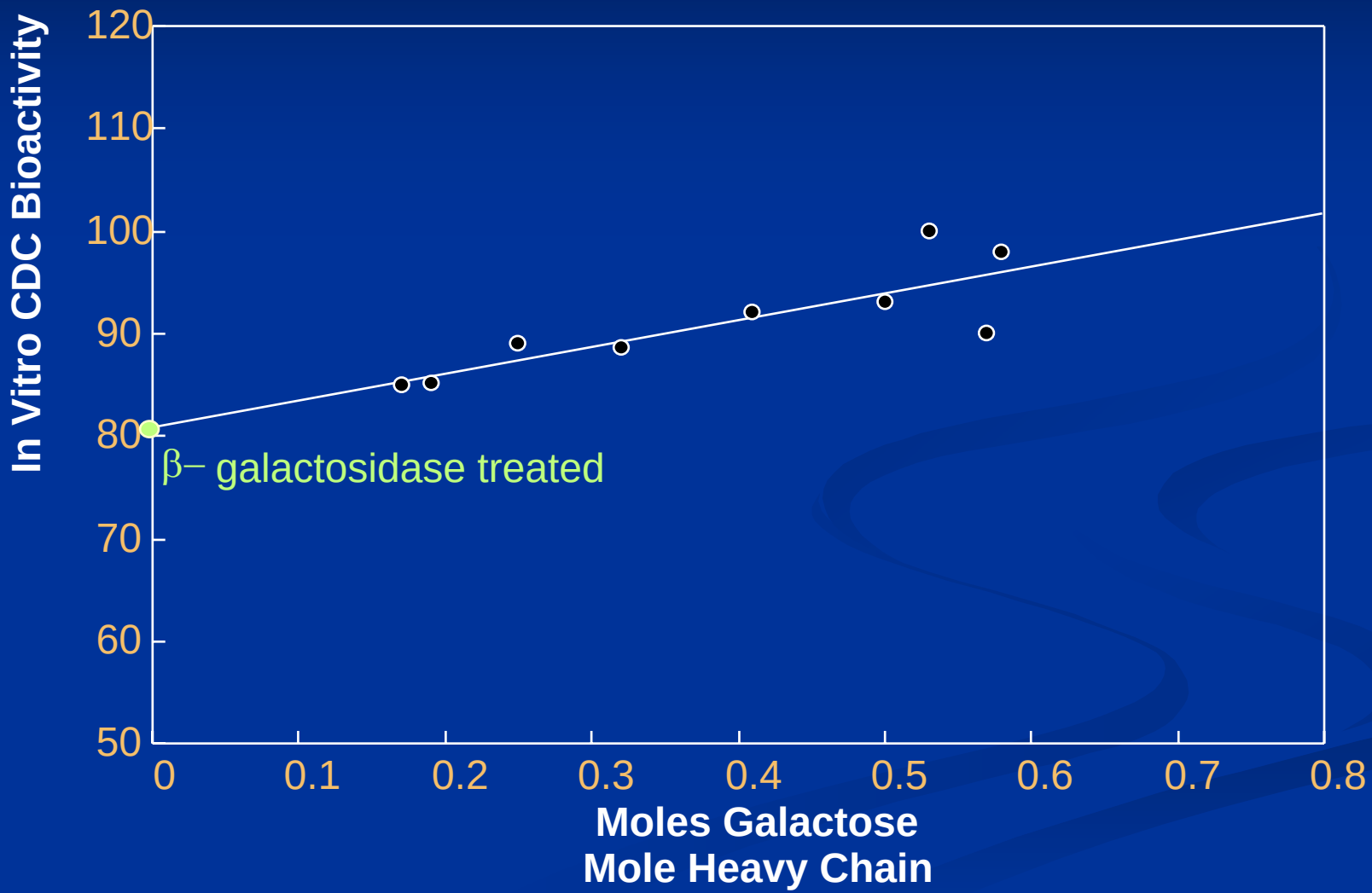
CE Analysis of Neutral N-Linked Oligosaccharides from a Recombinant Antibody



- Galactosylation variability is readily apparent
  - fucosylation (e.g., G0-F) may also be important

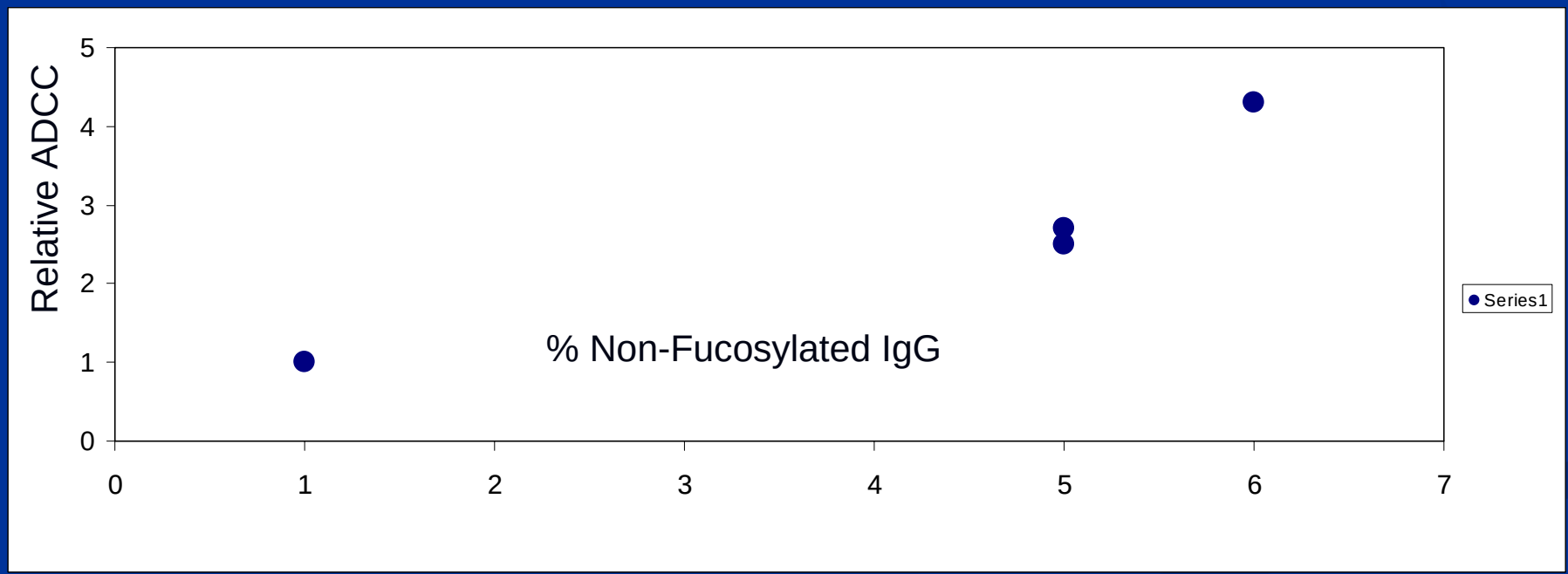
Reproducible and Robust Assay

Correlation of Bioactivity and Galactose Content in Rituxan™



When You Think You Know Everything...

- **Non-fucosylated Fc glycans : ADCC correlation unknown 5 years ago**
  - **very small differences may have significant *in vitro* effects:**



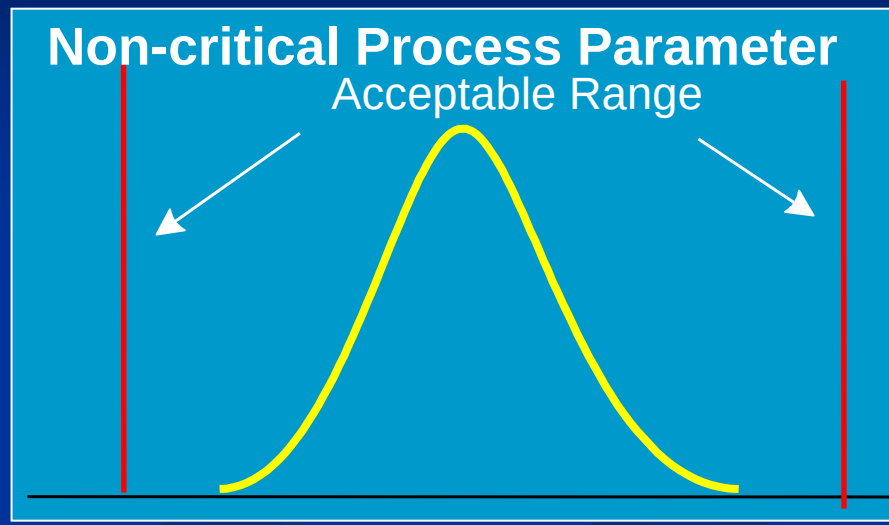
Evolution of Microbial and Adventitious Detection Techniques

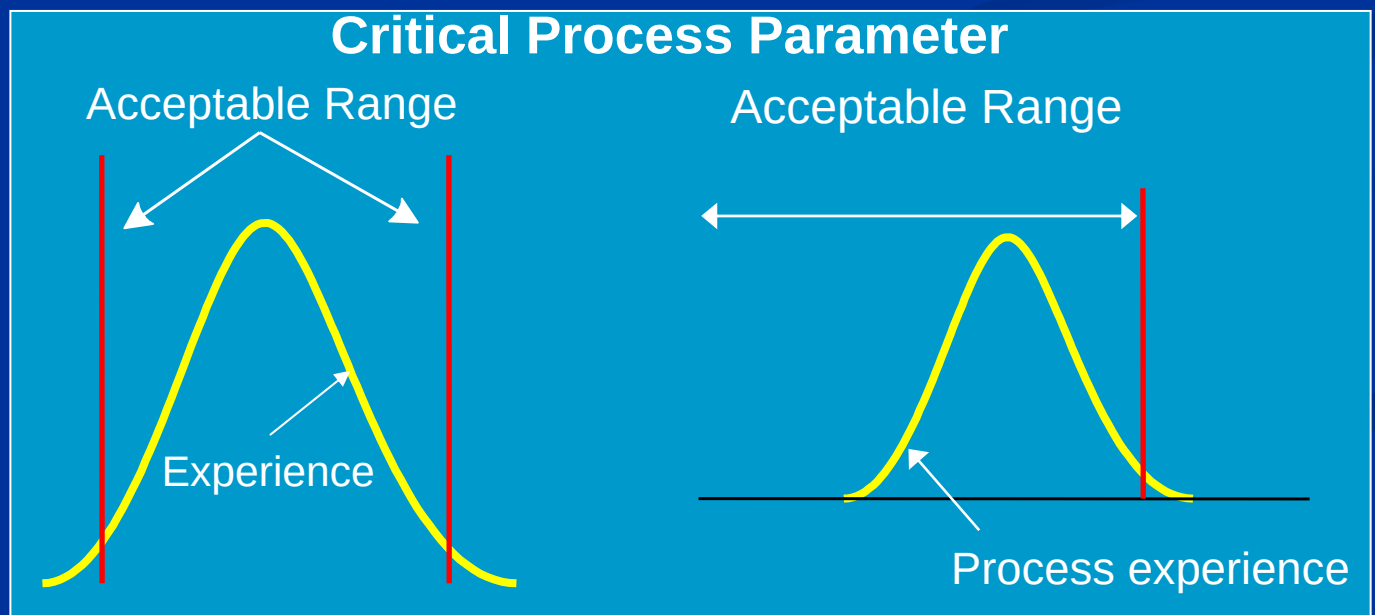
- 1900's to present:
  - Microbial and adventitious detection techniques based on amplification of low level contaminants using culture techniques
    - Lacks ability of timely contamination detection and control
      - Mycoplasma testing takes 28 days
      - Sterility testing requires 14 days
      - Bioburden testing requires 3-5 days
- 1985
  - Invention of PCR: Much faster and more sensitive detection

Evolution of Microbial and Adventitious Detection Techniques

- 2000-present
  - Real time microbial techniques are being developed and automated
  - PCR based adventitious agents testing has been approved (MMV) and/or submitted (mycoplasma) for regulatory approval:
    - High specificity and sensitivity
    - Dramatically improved cGMP compliance (8 hours vs. 28 days)
      - Detection of contamination well before facility is compromised
    - Potentially applicable to PAT analysis
    - Applicability to a broad range of adventitious agents

- **The Future of Biotech – Knowledge of Design Space will allow PAT to be used to achieve Quality by Design**
  - **Replaces traditional testing**
  - **Instantaneous release**
  - **Continuous processing**
  - **Reduction in cycle times**





The Future of Biotech

- **Technologies will be needed that are not available today - e.g., Process Analytical Technology / Control**
  - **Process controllers will use feedback/feed-forward loops to adjust the process parameters in real-time**
  - **On-line process analysis and control for:**
    - **Cellular metabolic parameters**
    - **Product identity and potency**
    - **Endotoxin**
    - **Adventitious agents, etc**

The Future of Biotech

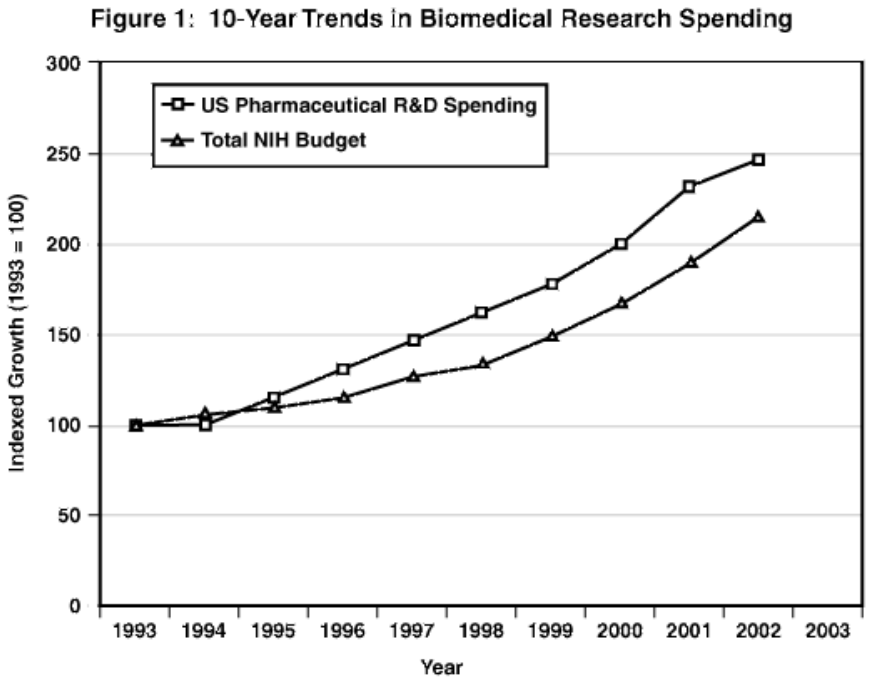
- Multi-product risks will be reduced
  - Disposables vs. cleaning

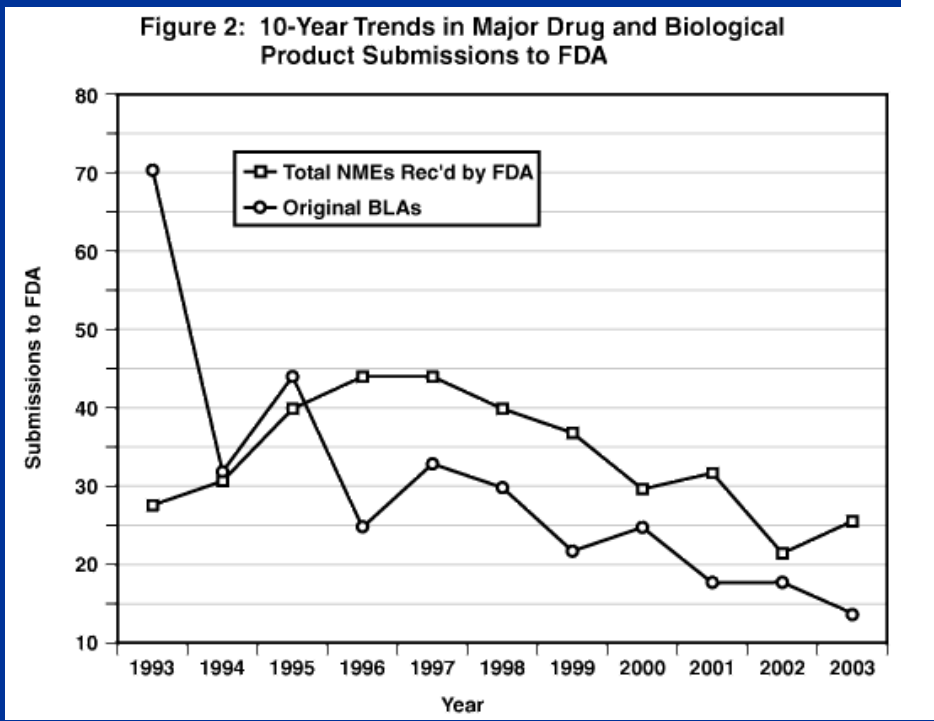
- Increased use of Global suppliers
  - Complex international sourcing of key raw materials, intermediates and active drug substance.

The Challenge…

Critical Issues

- Development costs continuing to rise
- Submissions declining





Message: We need to reverse these trends

The Industry

- Develop products for a global economy from the outset
  - Design space should be global
- Understand and attempt to meet all reasonable requests
- Communicate directly with the regulators or primary party license holders on a regular basis
- Influence regulatory thinking such that serious unintended consequences do not occur

The Regulators

- **Harmonization – ICH has not accomplished what was initially intended. Major issues have resulted adding unnecessary cost and complications to global filings.**
  - **Testing**
    - **Particulates**
    - **Sterility testing**
    - **Raw materials (EP, JP, USP)**
    - **Mycoplasma**
- **Region specific requirements are detrimental and result in unacceptable delays**
- **Submissions / Approvals**
  - **Process change categories**
  - **Risk management approach**
  - **QbD**
  - **Minimize reportable changes**

The Regulators cont.

- GMP's vs license requirements – differ between US, EU, Japan
- Consider unintended consequences carefully when requiring changes
- Country specific lot production is inevitably leading to untenable costs

Unintended Consequences

Case Study

- The Issue
  BSE – Prion concerns by global regulators over putative contamination of biotech products containing ungulate derived material, forces change to plant derived peptones and removal of all human and animal derived materials.
- The Intended Consequence
  Minimize or eliminate all risk to patients of prions from medicinal sources
- The Unintended Consequence
  Plant peptones substituted for animal peptones are found to contain acheoleplasma which propagate in cell culture media. The test takes 28 days and results in widespread production facility contamination.
- Removal of human albumin from EPO final product formulation in EU results in stopper leachables which react with EPO leading to PRCA (pure red cell aplasia).

Conclusion

- The Biotech Industry has been a great example of how regulators, the industry and academia have been able to work together to bring substantial improvements to the health of mankind. We are in a time of global interdependence and the need to work together to continue the success of this industry has never been more important.