



BIOTECanada
Vaccine Industry Committee

Current Challenges in Immunization

The Delicate Balance of Vaccine Supply & Demand

Presented by

Dr. Robert Van Exan, Ph.D.

Chair - Vaccine Industry Committee of BIOTECanada

Director of Immunization Policy – sanofi

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Vaccine Supply & Demand

The Fragility of Vaccine Supply

- ✓ Vaccines prevent disease and save lives
- ✓ Vaccines have eradicated smallpox and eradication of polio is imminent
- ✓ The success can be attributed to partnership:
 - *The vaccine industry* which has developed and produced most vaccines used today
 - Aggressive *public health* programs to immunize children and adults
- ✓ These successes are now threatened by systemic problems in the development, purchase and distribution of vaccines¹

Sloan et al. Fragility of the US Vaccine Supply, N Engl J Med 351; 23 Dec 2, 2004

Vaccine Supply & Demand

☑ Vaccine Supply

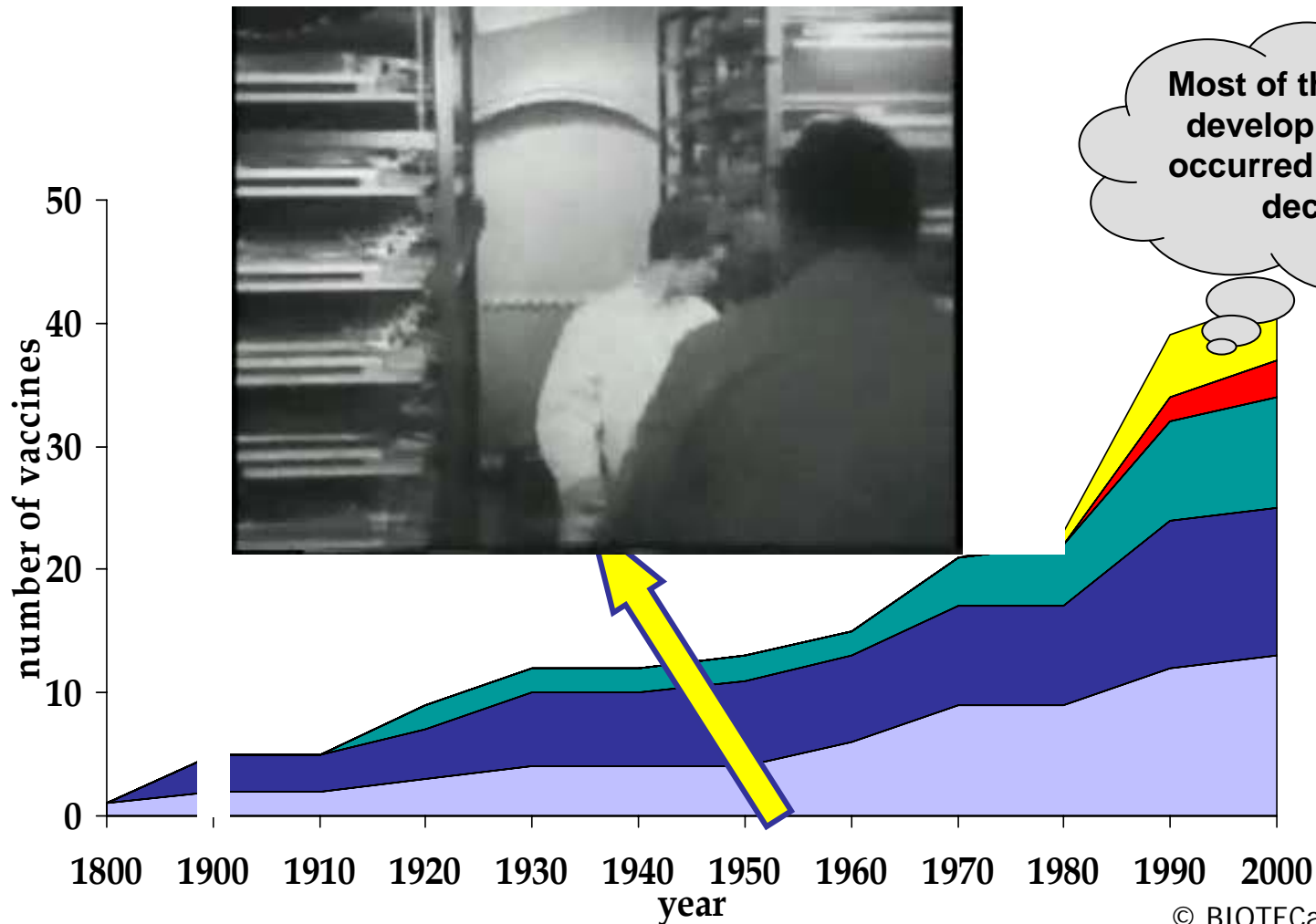
☑ Vaccine Demand

☑ Striking a Balance



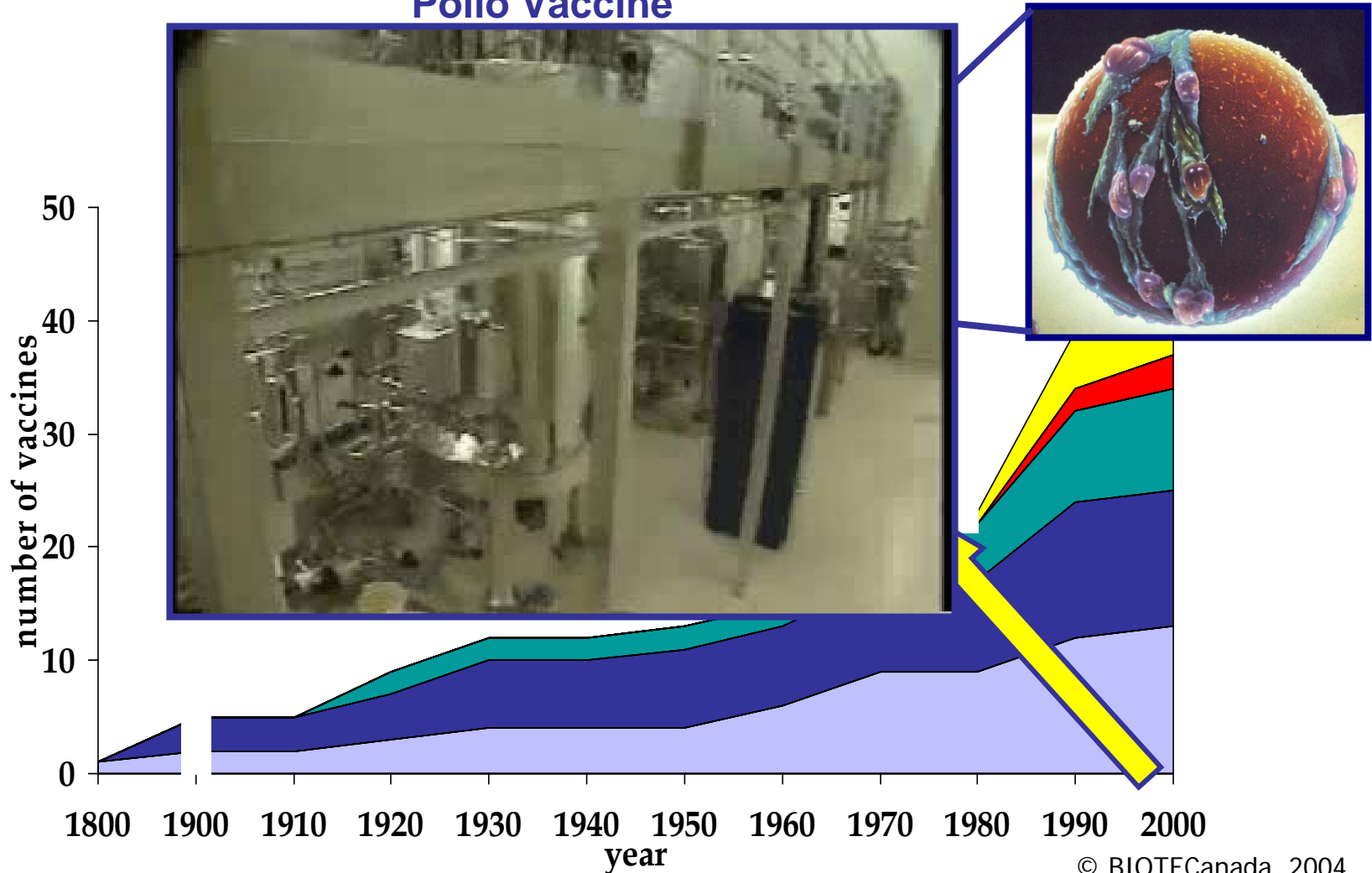
Vaccine Development From the 18th to 21st Century

Polio Vaccine

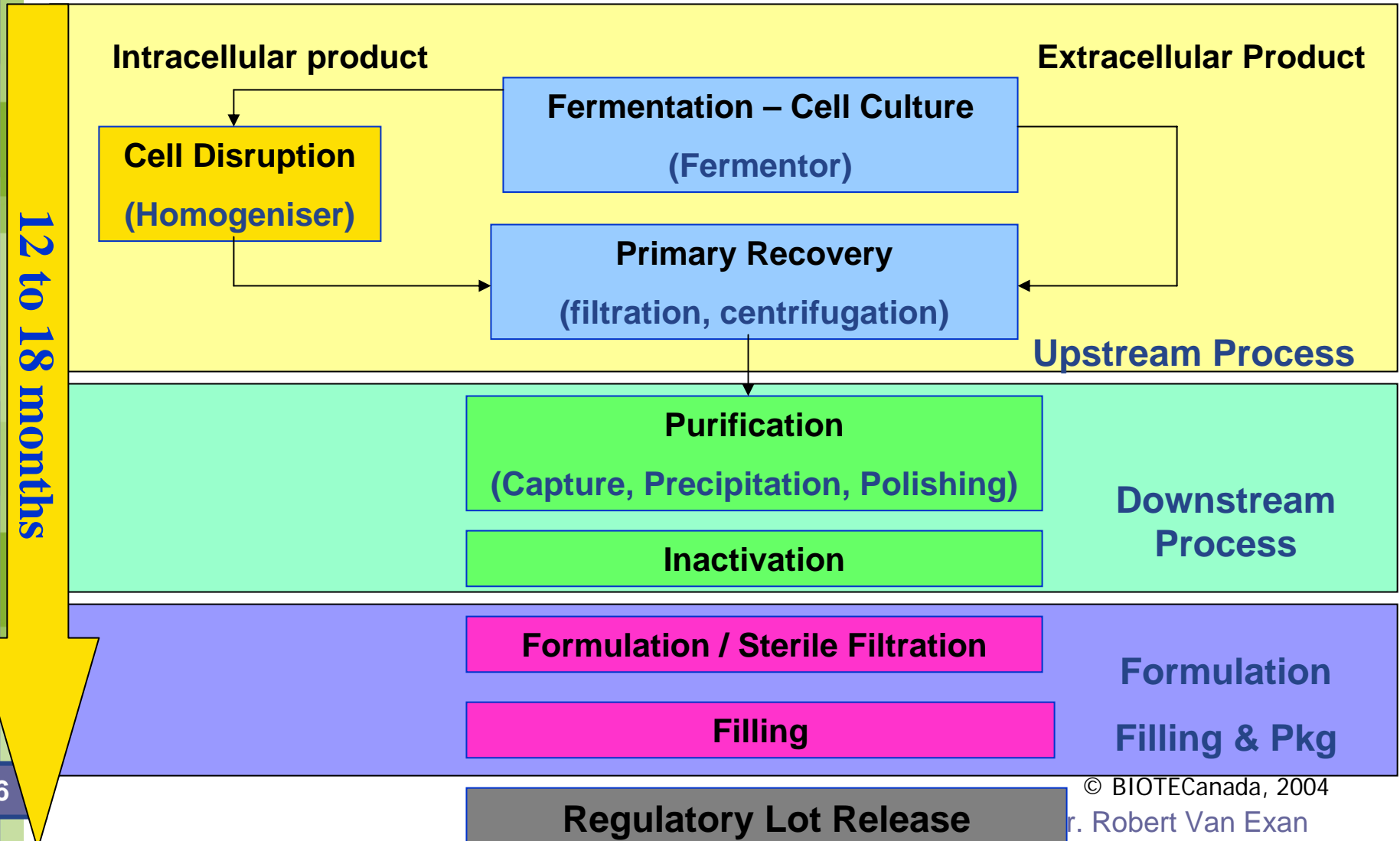


Vaccine Development From the 18th to 21st Century

Polio Vaccine



Vaccine Production



Cell Substrate

- Viral vaccines need a cell substrate
- Validated vaccine approved cell bank
- 2 to 3 years to validate
- 1 month to grow cells to production level



Upstream Process – Growth Phase



The Room

- Sterile
- Hepa filtered air
- Pressure balance
- Steam sterilization
- Sterile distilled water supply
- Gowning procedures

Quality Regulations: Three levels of barrier to protect the product

Upstream Process Primary Recovery

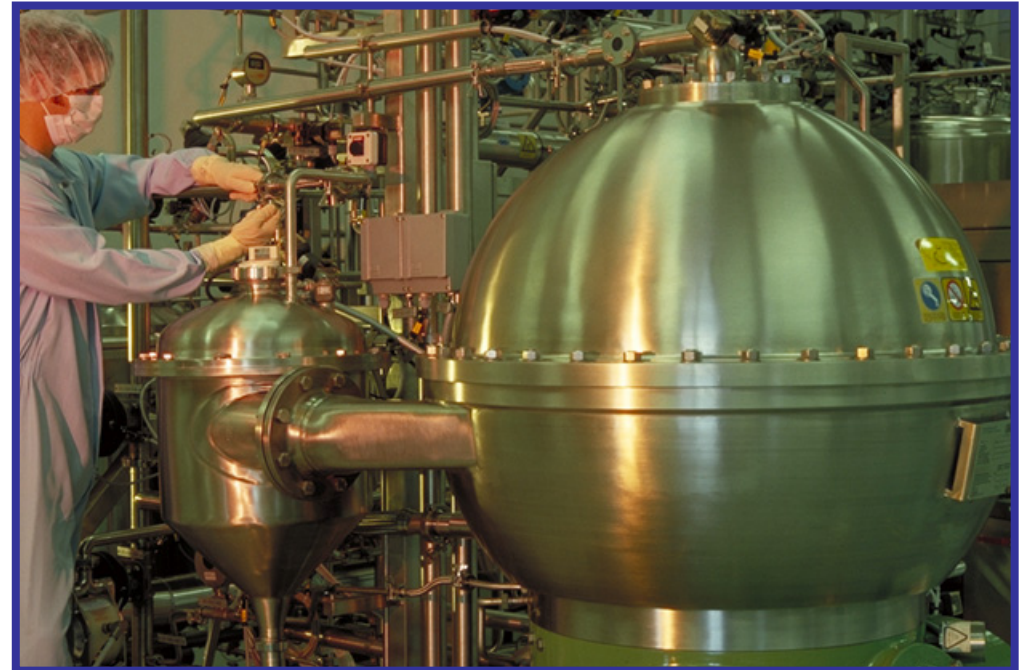
☑ Cell Disruption

- Mechanical
- Chemical

☑ Clarification

- Centrifugation:
- Filtration:
- Chromatography:

Clarifying centrifuge



Downstream Process

✓ Primary Objective:

- removal of impurities
- Maintain biological activity

✓ Secondary Objective:

- Clearance of adventitious agents

✓ Inactivation

- Chemical or physical
- BPL, formaldehyde, heat

Filtration



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Formulation

- **Dilution**
- **Adjuvant (eg adsorption to AlOH or AlPO₄)**
- **Stabilizers**
- **Preservatives**
- **Blending antigens**
 - Polio trivalent = type 1 + type 2 + type 3
 - Pneumococcal polysaccharide = 23 serotypes
 - Meningococcal polysaccharide = 4 serotypes
 - Pneumococcal conjugate = 7 serotypes
 - Acellular Pertussis = 1 to 5 different antigens (PT, FHA, Pertactin, Fim2, Fim3)
- **Combination Vaccines**
 - MMR = 3 vaccines (Measles, Mumps, Rubella)
 - Pentacel = 5 vaccines



Filling & Packaging

- ☑ Sterile filling
 - Liquid vaccines
 - Freeze dried vaccines
- ☑ Physical Inspection
- ☑ Labelling & Packaging
- ☑ Storage
 - 2-8°C
 - Frozen
- ☑ Shipping
 - Cold Chain

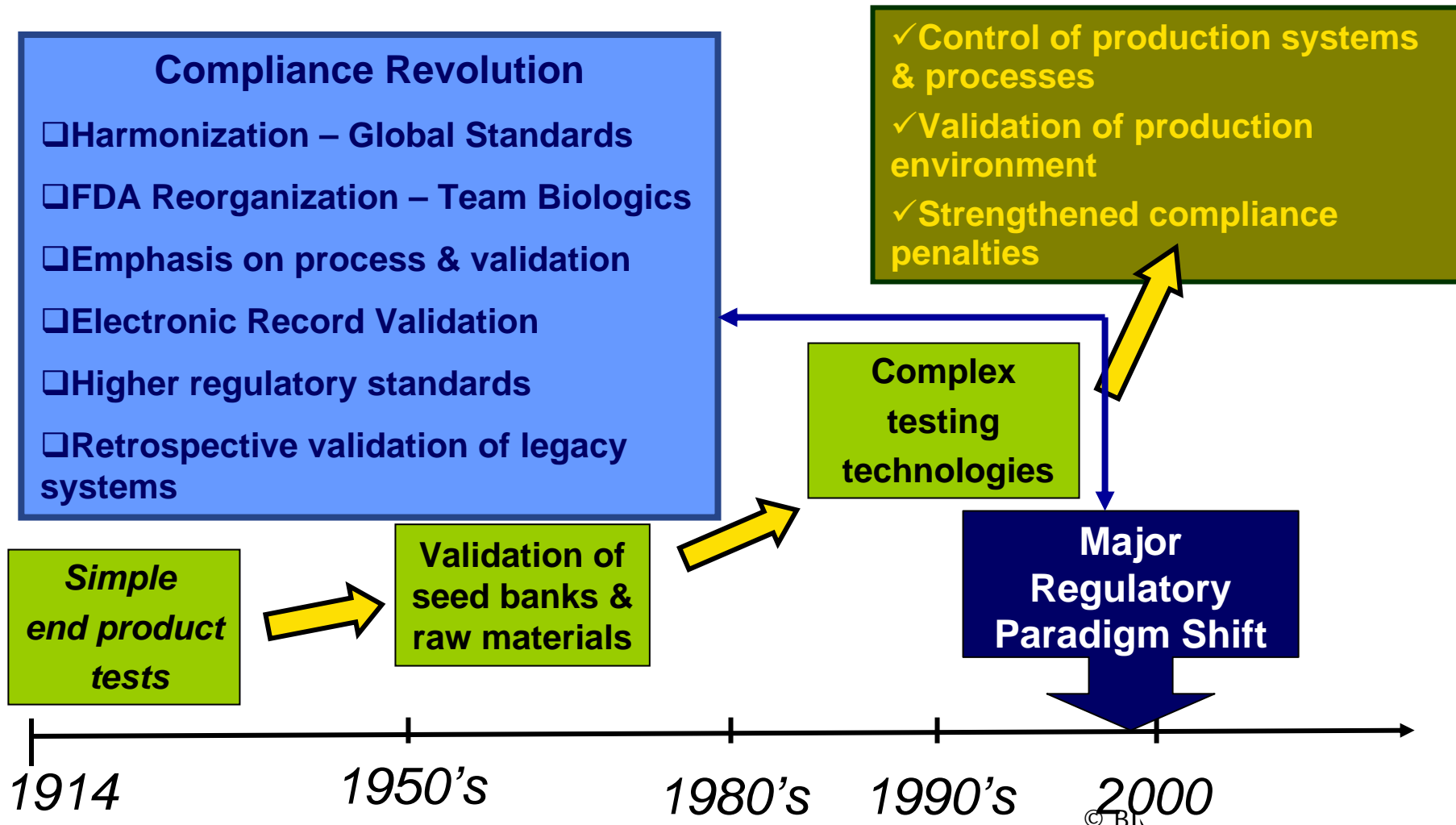


Quality Control



- Identity
- Quantity (specific activity)
- Purity (quantification of contaminants)
- Characterization (size, structure, sequencing)
- Activity (Immunology testing, in vitro based system)
- Potency in relevant animal model (correlates of protection)
- Microbial sterility, pyrogenicity, toxicity, general safety, etc.

Compliance Revolution A Paradigm Shift



Impact of Increasing Regulatory Compliance on the Vaccine Industry

☑ Lot Release

- Testing of every lot by manufacturer and regulator
- Lot failures

☑ Increased Regulatory Compliance

- increase production failures as regulations become more stringent
- reduced capacity
- increased production cost
- supply disruptions

☑ Increased Regulatory Penalties

- FDA “team biologics”
- Large fines
- Plant closures

Impact of Increasing Regulatory Compliance on the Vaccine Industry

Process Improvements and Process Change

- Removal of materials of animal origin
- Removal of blood products
- Removal of Thimerosal
- Increased cost of production

Cold chain disruption

- Increased cold chain monitoring – increased loss of shipments
- Increased cost of shipping

Removal of Thimerosal from DTaP vaccines

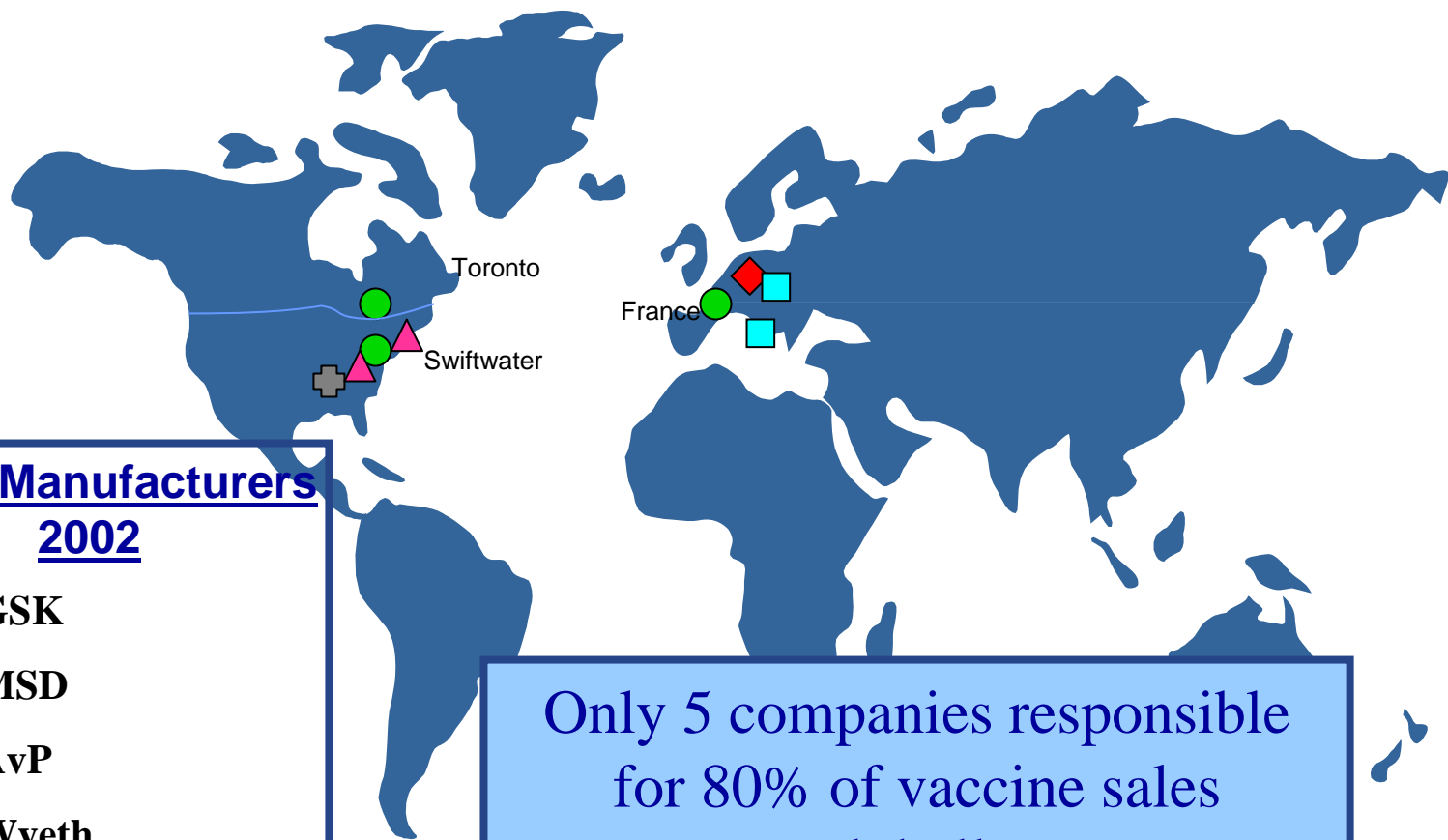
- ☑ Without Thimerosal only single dose vials possible
- ☑ Manufacturing process changed to ensure greater aseptic conditions for filling of single dose vial without preservative
- ☑ Manufacturing yields drop due to need to overfill every vial
- ☑ Reformulation requires re-licensing, a complex and lengthy procedure
- ☑ Net results: approximately 2 years of development work for an existing product and 25% reduced output

Impact of the Compliance Revolution

- ☑ Increased Vaccine Production Costs
 - Manufacturing Costs
 - Quality Control and Quality Assurance Costs
 - Manufacturing facility costs
- ☑ Reduced Capacity
 - WIP Losses
 - Longer production cycles
- ☑ Reduced Profitability
 - Plant closures
 - Companies leaving the industry



Global Vaccine Supply

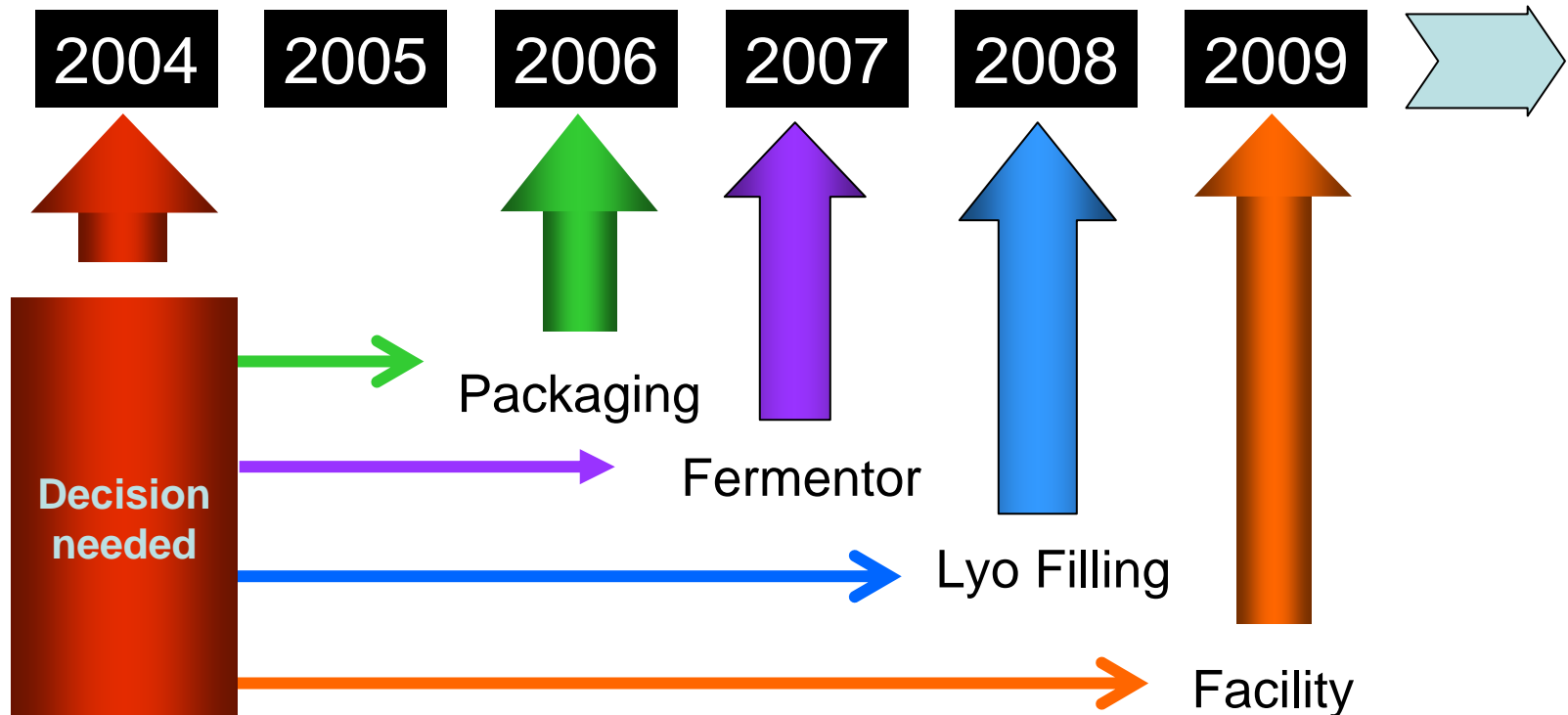


Top 5 Manufacturers 2002

- ◆ GSK
- ⊕ MSD
- AvP
- ▲ Wyeth
- Chiron

Only 5 companies responsible
for 80% of vaccine sales
globally

Timeline for Capacity Increase



Decision timeline for capacity increase

Vaccine manufacturing trends:

- ☑ Increased cost
- ☑ Reduced capacity
- ☑ Fewer suppliers
- ☑ Increased supply disruption



The imbalance between increasing manufacturing costs and vaccine prices has increased the fragility of vaccine supply

Vaccine Supply & Demand

- Vaccine Supply
- Vaccine Demand
- Striking a Balance



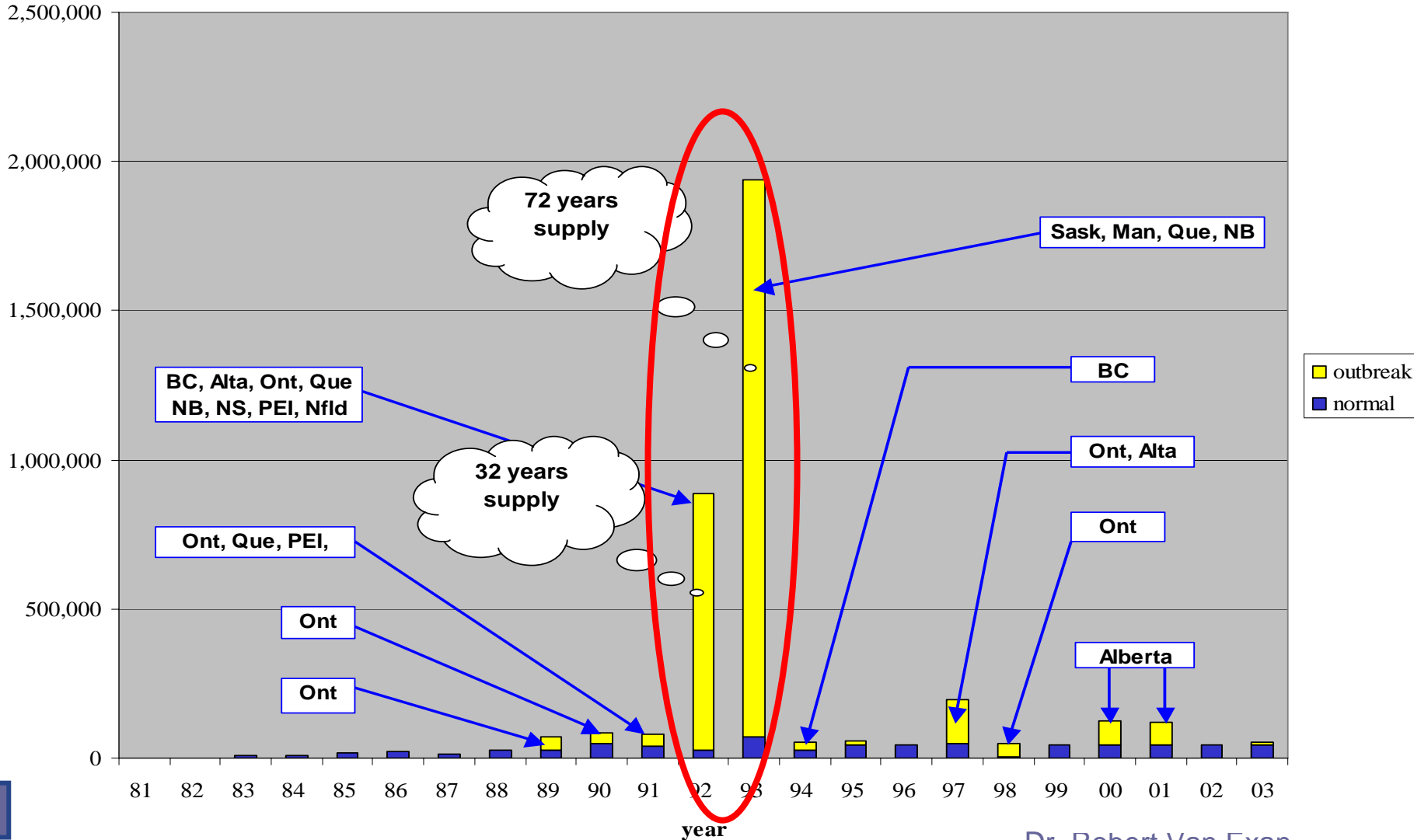
Factors Affecting Vaccine Demand

- ✓ Outbreaks, Emerging Diseases, Bioterrorism
- ✓ Public Awareness
- ✓ Cold chain
- ✓ Public Health Policy
- ✓ Purchasing Policy



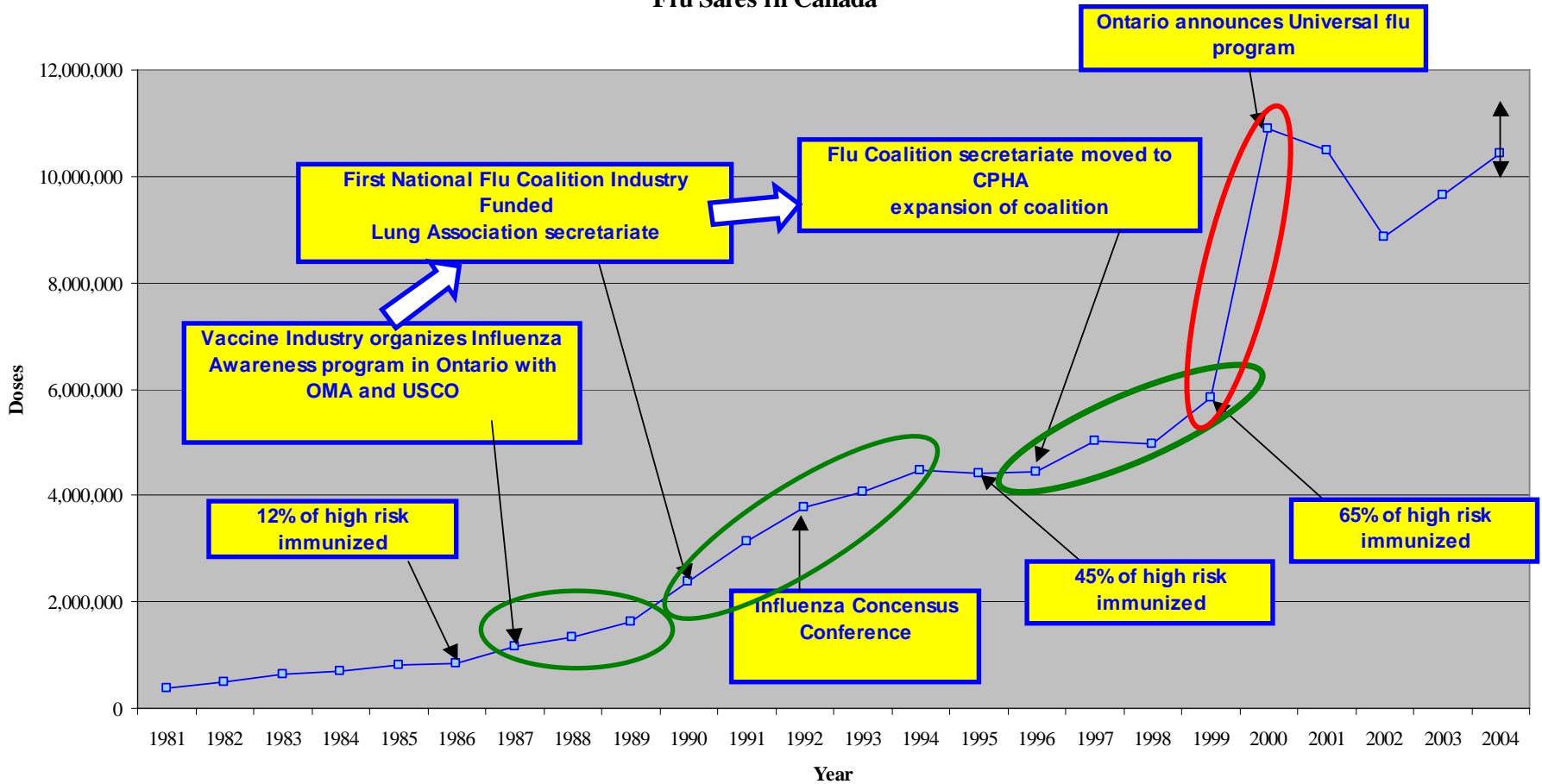
Ont

doses



Influenza Awareness

Flu Sales in Canada



Cold Chain

- ☑ Fragile cold chain distribution beyond manufacturer
- ☑ Vulnerability of vaccine in intermediate and end user refrigerators
 - Lack of Quality Assurance
 - Redundancy
 - Monitoring
- ☑ Examples of wide spread power failures:
 - Ice storm of 2000
 - Power failure – Ontario 2002
 - NS – Hurricane Juan, Snow storm Nov 2004

Public Health Policy and Demand

☑ **NACI recommendations**

- Changes in vaccine recommendations cause sudden changes in demand

☑ **Government Immunization Policy**

- Changes in government funding policy can create sudden changes in demand

☑ **Canadian Immunization Committee**

- Changes in goals and objectives of immunization programs can create sudden changes in demand

Purchasing Policy Supply and Demand

- ☑ No consideration for manufacturing lead times
- ☑ No consideration for manufacturing capacity
- ☑ Impact on manufacturing costs
 - Low price drives companies from market
 - Wasted production effort increases costs

Vaccine Procurement System in Canada*

Sector –	Public (provincial budget)
Structure –	Centralized (Vaccine Supply Working Group)
Method –	Monopsonistic (no other market for vaccines)
Strategy –	Tender, "winner take all"
Selection Criteria –	Lowest Price

Cost of Compliance?

Cost of Security of Supply?

Cost of Vaccine R&D?

Result: Canada has disproportionately low vaccine prices – extreme pressure on vaccine industry margins.

Is this the only procurement system?

There are other procurement methods that^{1,2,3,4}:

- ✓ focus on “reasonable price” for best value
- ✓ recognises and values research & development
- ✓ recognises unique highly technical products – not commodities
- ✓ recognises the need for security of supply
- ✓ creates an environment conducive to the manufacturers and Public Health

1 “Guide to drug financing mechanisms” WHO 1998, Geneva

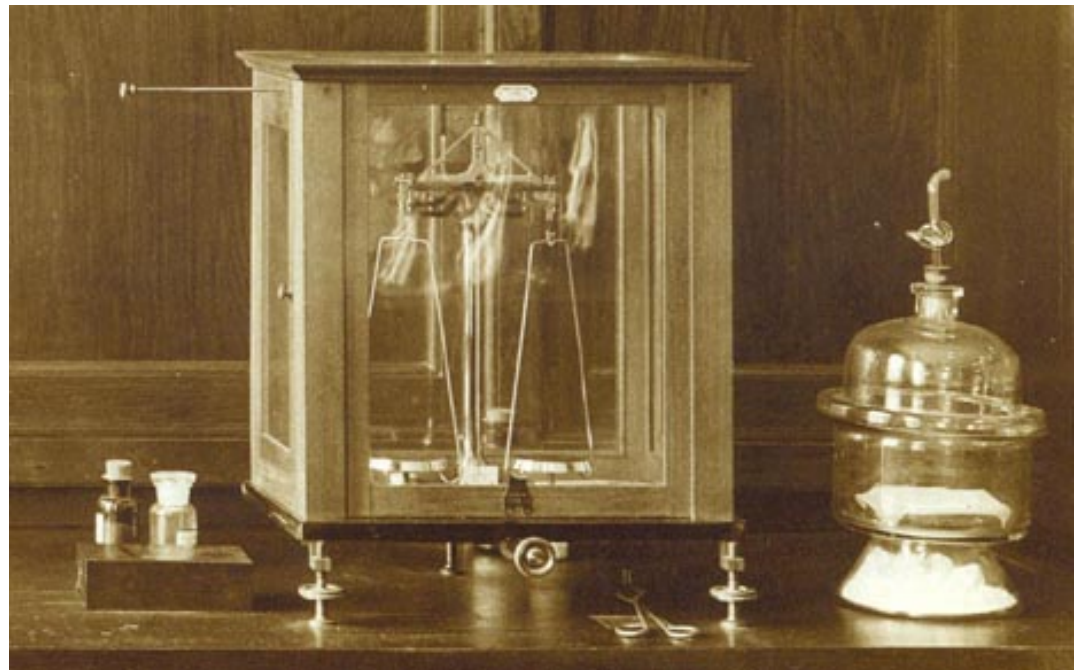
2 Institute of Medicine. Financing Vaccines in the 21st Century, 2003

3 Rappuoli, Miller & Falkow, Science, vol 297; Aug 2002

4 Sloan et al. The Fragility of the US Vaccine Supply. N Engl J Med 351;23 Dec 2004

Vaccine Supply & Demand

- ☑ Vaccine Supply
- ☑ Vaccine Demand
- ☑ Striking a Balance



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Key Issues

Supply



- ✓ Number of Suppliers (Few)
- ✓ Production lead time (12 – 18 mo)
- ✓ Capacity lead time (2 – 5 yrs)

Collaboration,
Communication,
Planning

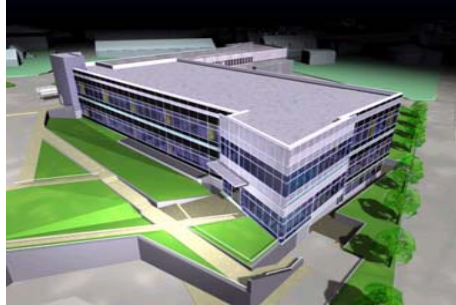
Demand



- ✓ Rapid changes in demand
 - Outbreaks, Emerging Diseases, Public Demand, Cold Chain etc
- ✓ Policy Changes
- ✓ Purchasing Process

Collaboration,
Communication,
Planning

Industry/Government Collaboration



**Negotiation
Procurement Reform**

**Aligned Objectives
Mutual Benefit**



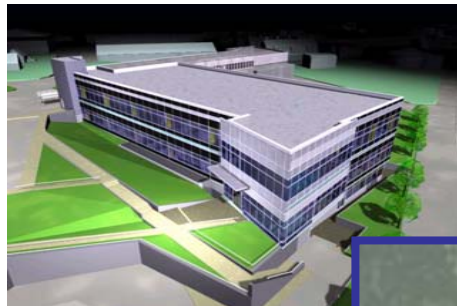
**Shared Responsibility
Communication**

**Partnership
Joint Planning**

**Regulatory
Change**

Aligned Objective & Joint Investment

Industry Government Collaboration Partnership



**“We are walking on the same road in a deepening fog...
....why not walk together”**