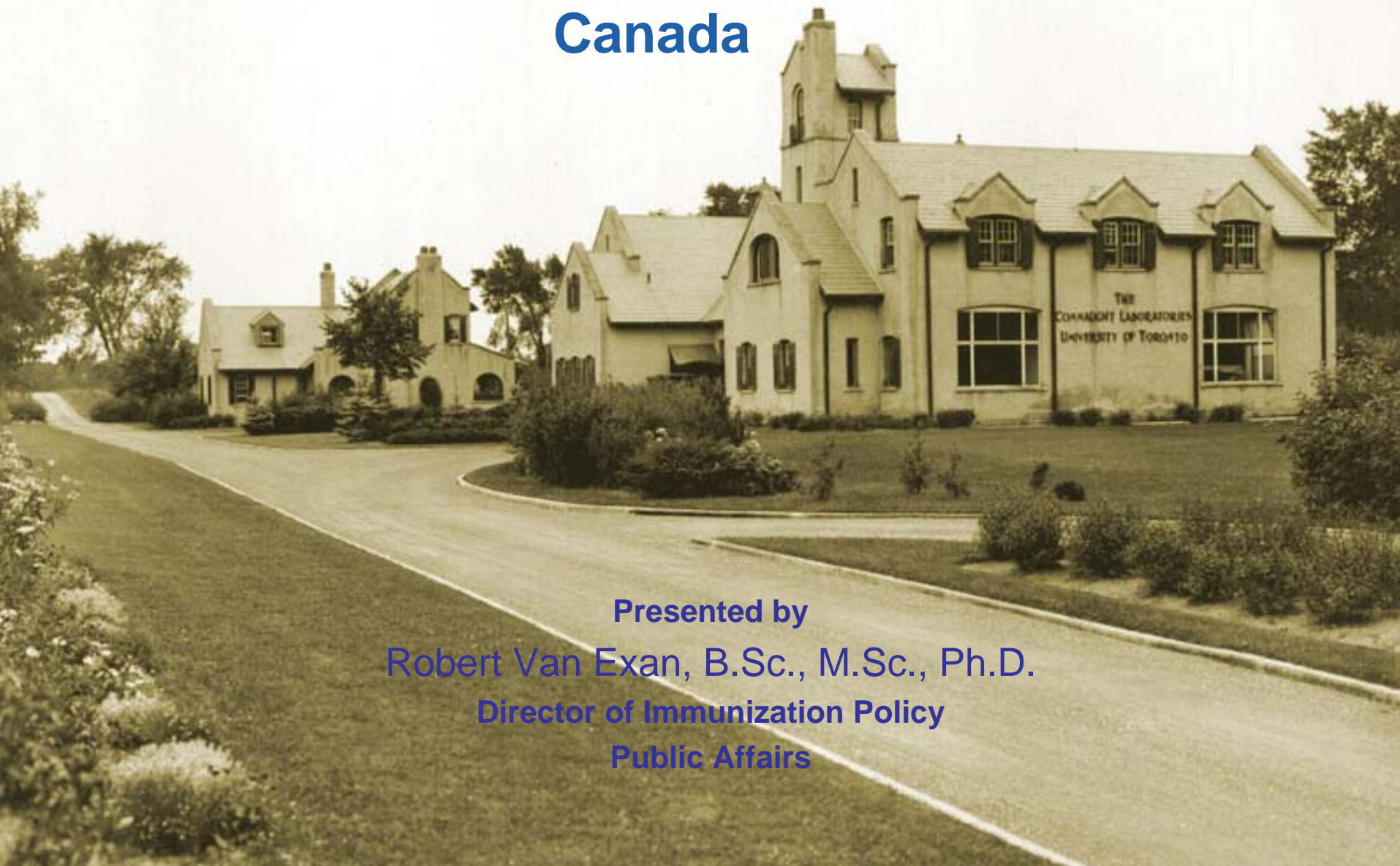


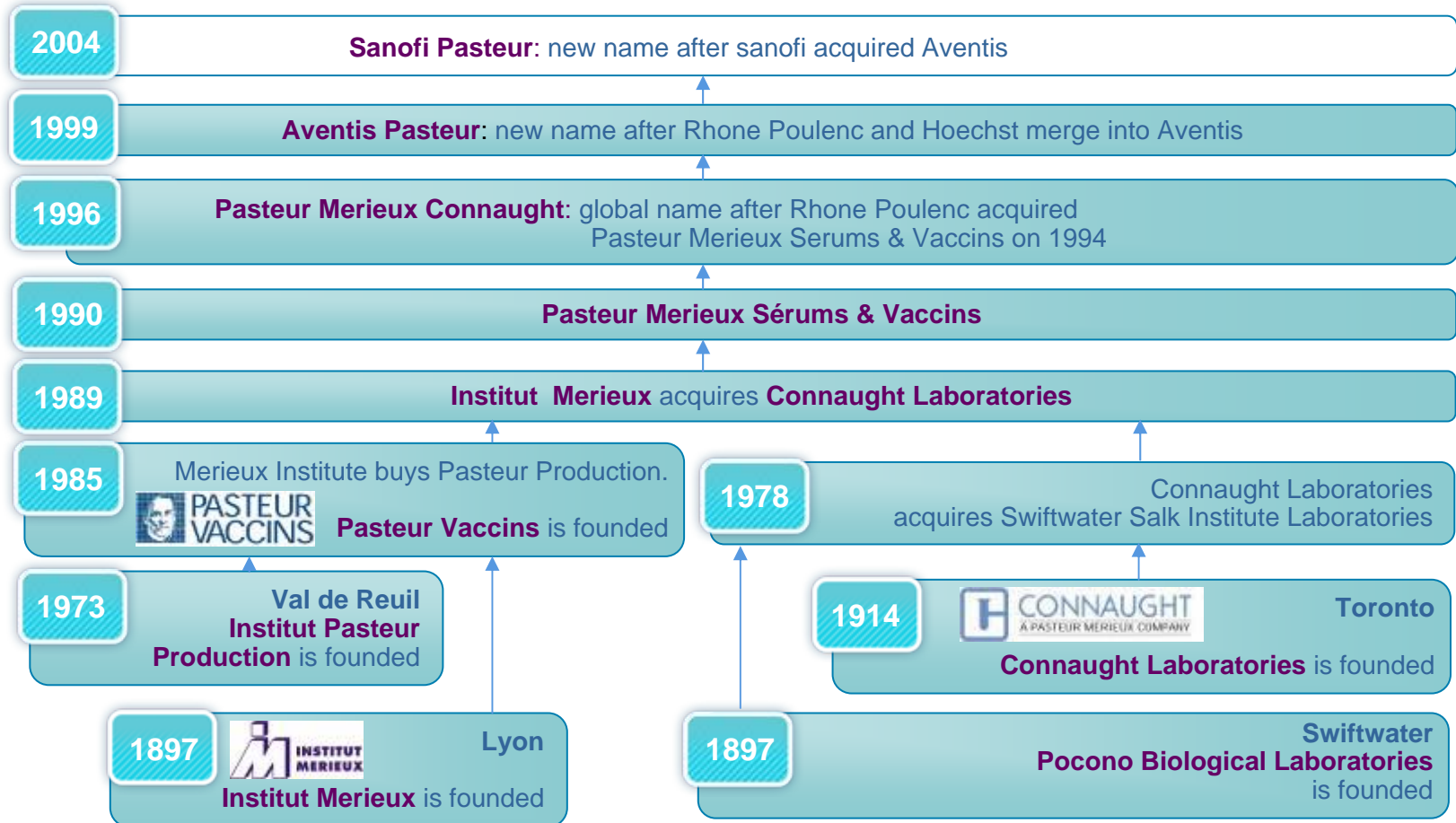
Sanofi Pasteur:

95 Years of Vaccine Manufacturing in Canada



Presented by
Robert Van Exan, B.Sc., M.Sc., Ph.D.
Director of Immunization Policy
Public Affairs

Sanofi Pasteur's heritage



Overview of sanofi pasteur in Canada



Two Locations

- **Connaught Campus:**
1,040 employees

Connaught Campus

(located at Steeles & Dufferin)



- **Sunnybrook Campus:**
60 research scientists



Sunnybrook Campus

(Sunnybrook & Women's College Health Sciences Centre)

Overview of sanofi pasteur in Canada



Research & Development:

- ❑ 250 employees
- ❑ Research, Development, Clinical, Medical and Regulatory

Industrial Operations:

- ❑ 600 employees – uniquely skilled and highly educated workforce
- ❑ 200 million doses/year to international markets

Commercial Operations:

- ❑ 150 employees – Sales, Marketing, Public Policy, and Legal
- ❑ 25 products – 14 million doses of vaccines/year in Canada



History:

- Originated as Connaught Laboratories in 1914 at the Hygiene Department of U of T
- Opened manufacturing facility in 1917 on 150 acre farm at Steeles & Dufferin
- Dr. John Fitzgerald (Canadian Medical Hall of Fame) was the first director



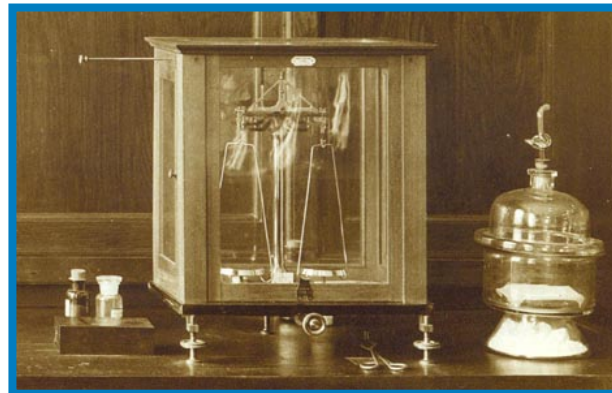


History:

- Originated as Connaught Laboratories in 1914 at the Hygiene Department of U of T
- Opened manufacturing facility in 1917 on 150 acre farm at Steeles & Dufferin
- Dr. John Fitzgerald (Canadian Medical Hall of Fame) was the first director
- Historical Contributions – Biologicals of Medical significance

Biologicals

- ✓ Antitoxins
- ✓ Insulin
- ✓ Epinephrine
- ✓ Heparin
- ✓ Plasma Fractionation
- ✓ Penicillin



Vaccines

- ✓ Pertussis vaccine
- ✓ Polio vaccine
- ✓ Smallpox vaccine
- ✓ Acellular pertussis
- ✓ Combination vaccines
- ✓ Influenza vaccine

1918-19: Influenza Pandemic

JOLLY'S DRUG NEWS.

No Need To Catch Spanish "Flu"

Cutter's Respiratory Vaccine is a sure preventive.

We are completely sold out today but a very large supply is on the way.

It will come in serial doses and prophylactic syringe doses.

To the Busy Doctors

Telephone or telegraph your requirements and supplies will be forwarded to you immediately on arrival.

Jolly's Cash Drug Store

1821 SOUTH RAILWAY STREET, REGINA, SASK.

Phone 3606 Opp. Union Station

"The Safe Place to Send Your Prescriptions"

Enterprising pharmacists were soon advertising the new vaccines. (The Leader, Regina, Saskatchewan, October 31, 1918. Photo courtesy Saskatchewan Archives Board)

Widespread Ravages of Spanish Influenza and Consequent Diseases

In Montreal Alone There Are 20,000 Cases of Influenza and From All Points Come News of Its Spread.—In Halifax We Have 500 Cases.

MONTREAL, October 12.—It is estimated that there are nearly twenty thousand cases of grippe in Montreal and still more stringent regulations are enforced by the board of health to curb the epidemic. The order follows:

"All stores, shops, and bars of all kinds, retail and wholesale, except drug stores (for sale of drugs only) butchers' shops, grocery stores shall close at four o'clock.

"All churches, theatres, moving picture houses, dancing halls, billiard and pool rooms, bowling alleys, public baths, auction rooms, assembly or lecture halls shall remain closed.

"No athletic sports, sporting gatherings of any kind or meetings open air or otherwise, where more than 25 people gather shall be allowed.

"All schools, public or private, including Sunday schools shall remain closed.

"Boarding schools shall not be allowed to receive or entertain visitors and if allowed leave of absence pupils shall not be allowed to re-enter the school.

"Public offices including banks, government offices, municipal offices shall close not later than 4:30.

"All hospitals and dispensaries (except in urgent cases) shall be closed to all but emergency cases.

"No public shall be admitted to the courts except those essential to the prosecution of the cases called.

"The board recommends most especially to the public not to crowd into any frames; and to avoid as much as possible any crowded train, tramway or railway station."

TORONTO, October 12.—Spanish influenza continues its steady advance thru every district of the city and province. The hospitals are practically all filled and the department of health in considering taking over some of the vacant hotel properties for additional hospital accommodation. Advertisements are in the press for voluntary nurses as nurses, maids, orderlies, etc. to strengthen the forces which are busily fighting the epidemic. Dr. Hastings has ordered all conventions and other large gatherings to be postponed until epidemic abates. Among the conventions which will be cancelled are the Baptist convention of Ontario and Quebec, planned to open on Wednesday; the national association of electrical contractors and dealers, scheduled to start Monday; the three day conference of Local church workers "On Behalf of the Poor" arranged for next week. The Ontario Sunday school convention has been planned for October 21. An order has been issued that only immediate relatives shall be allowed to attend funerals of persons who have died from influenza. To prevent the development of epidemics in the wards of hospital for

cases, visiting has been disallowed during the epidemic. The same results has been taken at the other hospitals.

TORONTO, October 12.—Toronto academy of medicine issued following appeal:

"In view of urgent demands for nurses in care for civilian and military sick and for hospital accommodation the council of the academy appeals: That all nurses who are at present not engaged in nursing, should report themselves for duty without delay to the nearest facility, to the lady superintendent of the hospital, or to the medical authorities." At General Hospital thirty nurses are suffering from influenza. One of them is Miss Hope Aylsworth, nurse of Sir Aylsworth, Her condition is critical.

NEW YORK, October 12.—The request of public health has made it a misdemeanor for any person to cough or sneeze in a public place anywhere in the state of New York without covering the mouth or nose. Violators will be rightly prosecuted. The punishment will be \$100 fine or one year in prison or both. It was decided to make influenza a reportable disease, which means that every case must be reported to the health officers by doctors, hotel proprietors, boarding house keepers and householders. Every new case will be traced immediately under state control. From September 1 until today there have been 25,682 cases of influenza in New York city, and 2,552 cases of pneumonia. Deaths from influenza numbered 1,052 and from pneumonia 1,595.

CAPETOWN, October 12.—The worst plague that ever visited South Africa was nothing in comparison with the present epidemic of influenza. As a result of the epidemic there were 146 deaths in Natal during the week. The spread of influenza is diminishing in mining districts, where the hospital cases have been reduced from 20,000 to 2,000. Eight thousand cases have been reported at Durban. Some coal mines in Natal have been closed.

Five Hundred Cases Of Spanish Influenza Are Now in Halifax

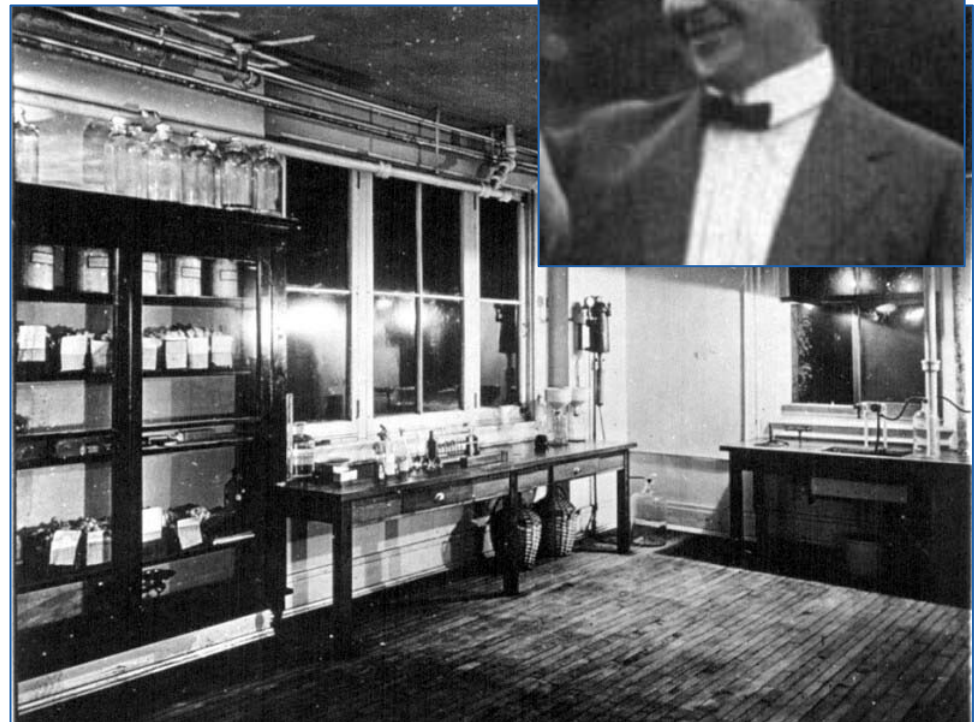
HALIFAX, October 14.—The fight against the spread of Spanish influenza by the city health board continues unabated with encouragement and comparison with other Canadian cities, and shows daily that the precautions measures taken in the early stages were fully justified. While the disease had made considerable advance during the past week, it has not been nearly as alarming or disturbing as it would have been had not effective means been adopted by the health board, before the epidemic stage was reached. Prospects are still

Newspapers of the day carried alarming reports of the spread of the disease. (The Halifax Herald, October 14, 1918. Photo courtesy Public Archives of Nova Scotia)

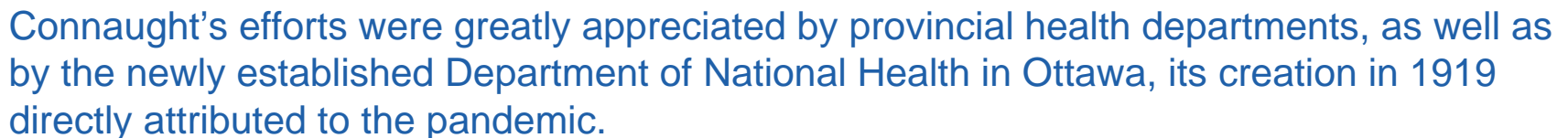
1918-19 – Connaught Supplies an Influenza Vaccine to the Nation

- During the pandemic there were frantic efforts to identify the cause of the disease and hopefully prepare a vaccine that might prevent it.
- Scientists had first targeted a bacterium, *B. influenza*, as the cause of influenza in 1892 and then prepared a vaccine based on a variety of strains isolated from influenza cases.
- Working day and night in a cramped lab, a small team under the direction of Dr. R.D. Defries, supplied Connaught's influenza vaccine free of charge, to provincial health departments, hospitals, the military and other public health services across the country.

Dr. Robert D. Defries

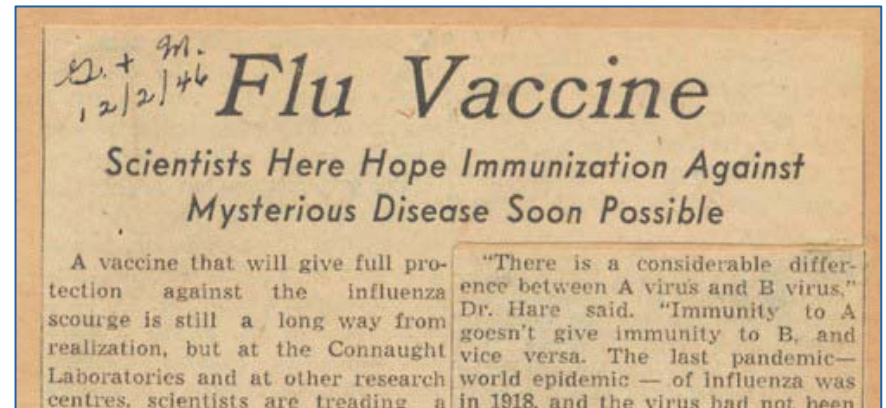


- Due to this unprecedented emergency, Connaught made no claims for the effectiveness of the vaccine, but kept careful records so that it could be evaluated.



1943-46: Connaught & Modern Influenza Vaccine Development

- Modern understanding of influenza began in the early 1930's when the virus was first isolated and cultivated in chicken eggs.
- The virus is then inactivated with formaldehyde to make a vaccine.
- There are three main types of influenza virus, but with many strains that change from year to year.
- This variability means that the vaccine has to be modified every year in order to prevent influenza outbreaks



1957: Influenza Vaccine – Pandemic Preparations

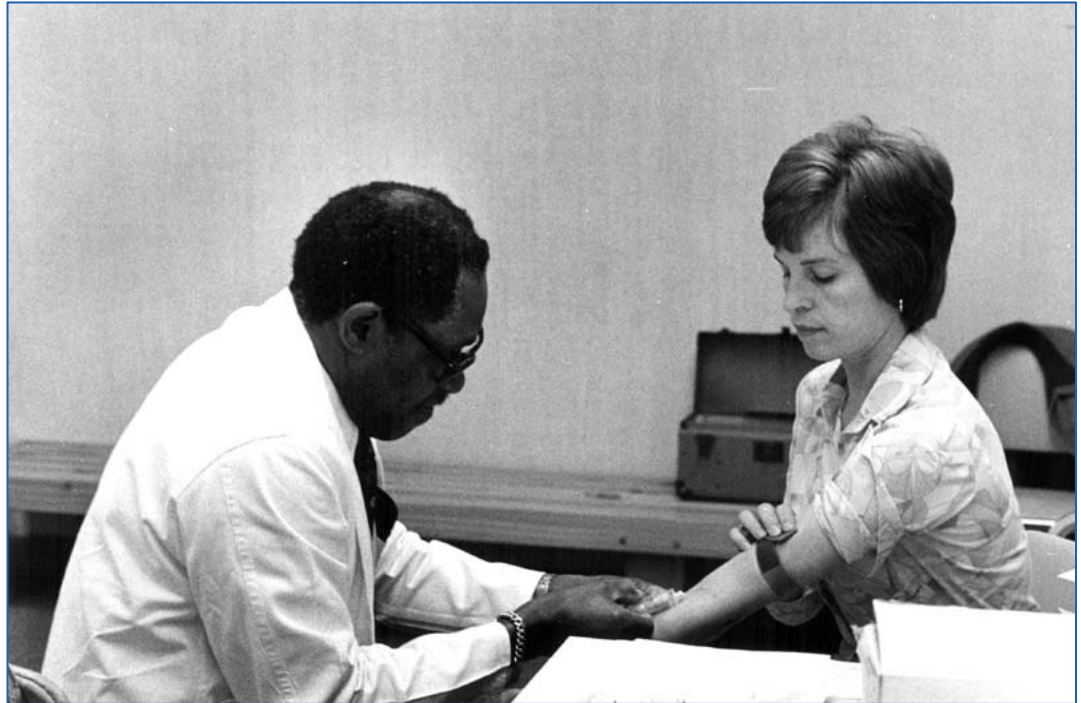


The most serious influenza pandemic since 1918-19 was in 1957, sparking the emergency production of influenza vaccine at Connaught Laboratories on behalf of the federal and provincial governments in Canada

*Chickens Help Doctors
Fight 'Walkabout' Flu*

1976: “Swine Flu” Pandemic Preparations

- Fears of another influenza pandemic developed in 1976.
- Fortunately this “Swine Flu” emergency did not materialize, although a large vaccine production and vaccination effort was launched in North America.



In Canada, Connaught Laboratories packaged bulk influenza vaccine supplied from a British manufacturer and conducted clinical trials that involved employee volunteers.

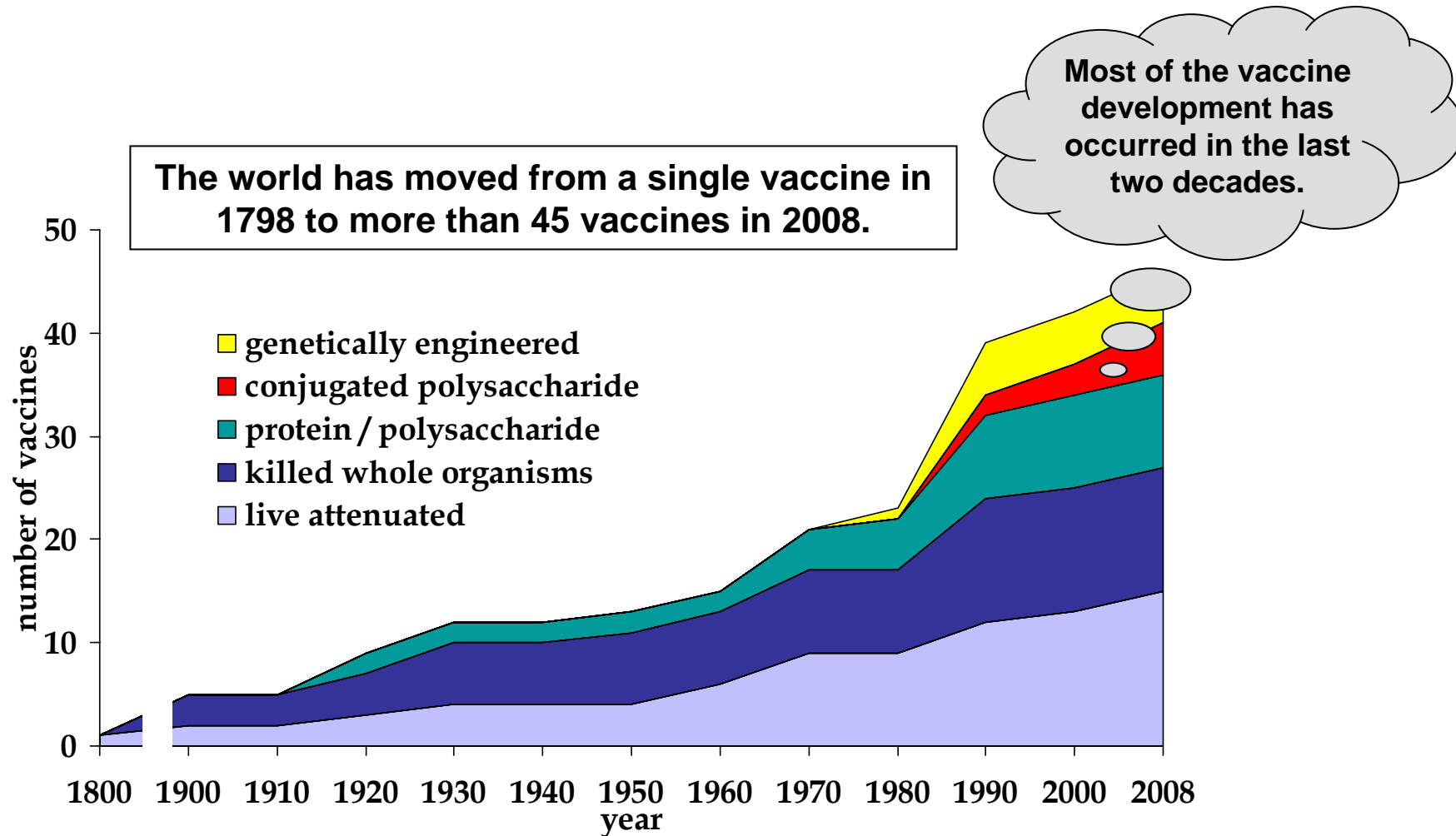
The History of Vaccine Development

Man's First Vaccine

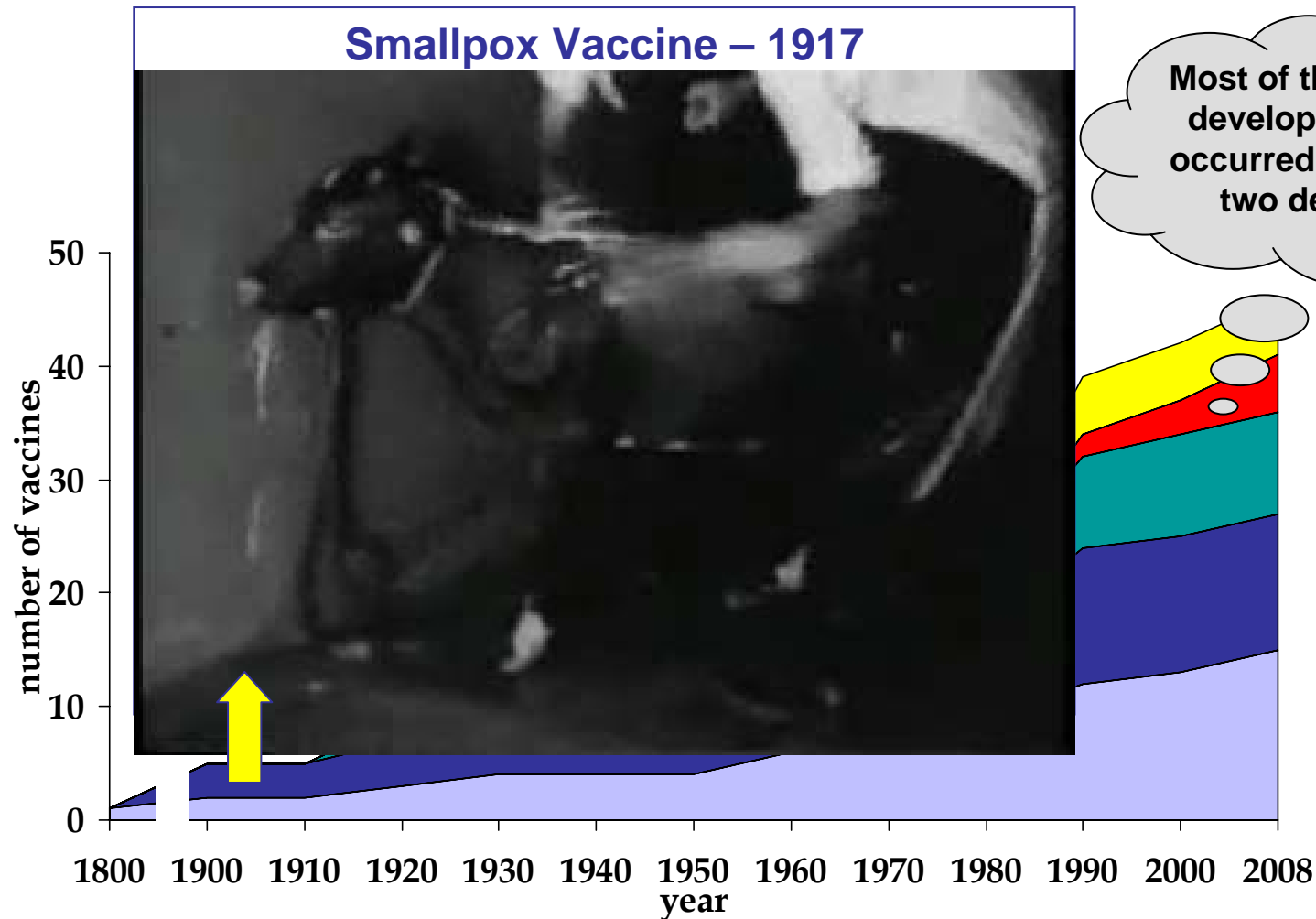
- ✓ Efficacy?
- ✓ Safety?
- ✓ Delivery?
- ✓ Research Cost?
- ✓ Development Cost?
- ✓ Manufacturing?



Vaccine Development From the 18th to 21st Century

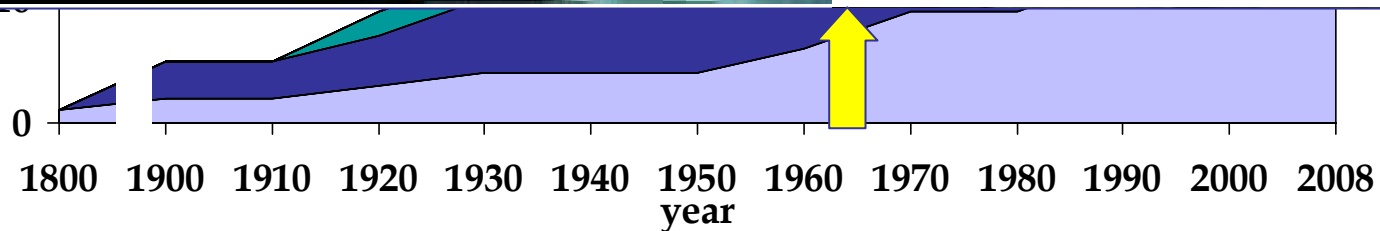


Vaccine Development From the 18th to 21st Century



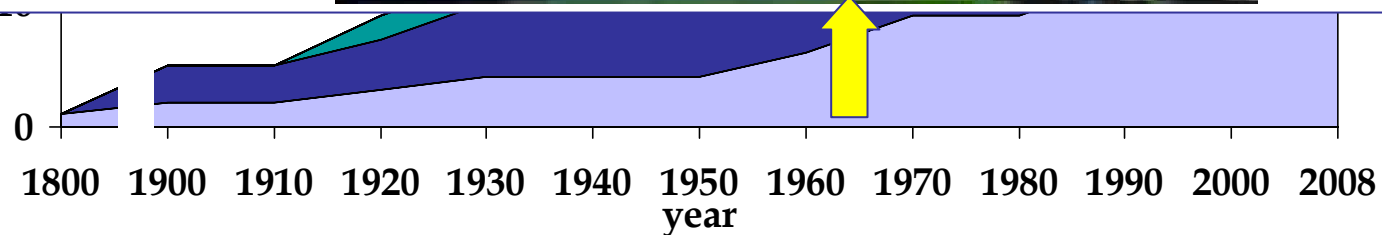
Vaccine Development From the 18th to 21st Century

Smallpox Vaccine – 1966



Vaccine Development From the 18th to 21st Century

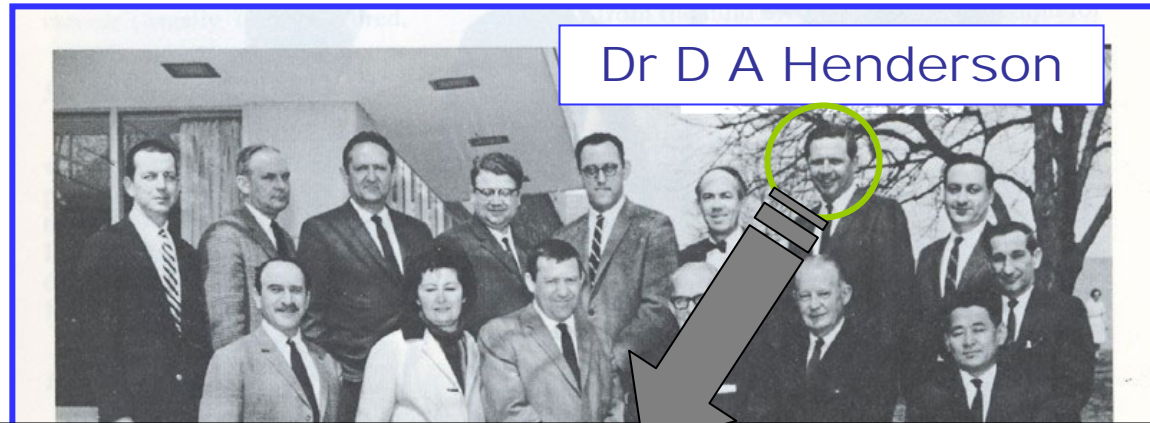
Smallpox Vaccine – 1966





Major Contributions:

● Eradication of Smallpox



Dr D A Henderson

"I appreciate only too well how many of the concepts in the execution of the smallpox program saw the first light of day over a glass of beer with Bob [Wilson] and Paul [Fenje]."

What I don't recall is whether the ideas stemmed from Wilson or Fenje, so perhaps they are better attributed to Wilje (or should it be Fenson?)."

D.A. Henderson to P. Fenje, June 18, 1979

Dr Paul Fenje

Dr R. J Wilson

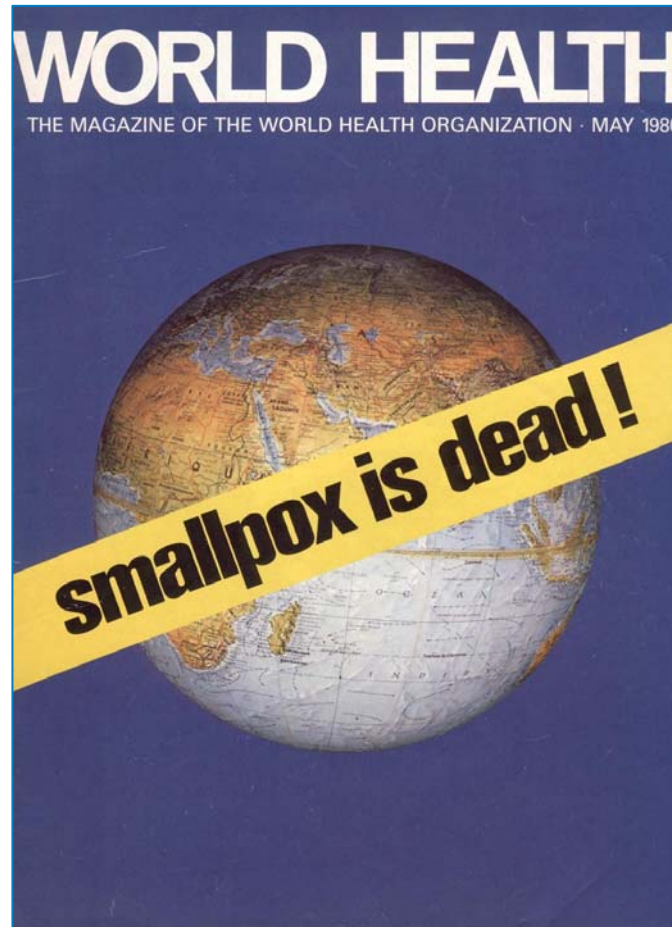
Plate 11.4. Members of the Seminar on Vaccine Production, at the final meeting from 28 to 30 March 1968, at the Wyeth Laboratories, Philadelphia, Pennsylvania, USA. Left to right, front row: P. Fenje (Canada), S.S. Marennikova (USSR), A.C. Hekker (Netherlands), J.H. Brown (USA), R.J. Wilson (Canada) and I. Arita (WHO); back row: F.M. McCarthy (USA), M.Z. Bierly (USA), H. Tint (USA), V.N. Milushin (USSR), A. Bernstein (USA), C. Kaplan (United Kingdom), D.A. Henderson (WHO), B.A. Rubin (USA) and A.K. Fontes (USA).

WYE

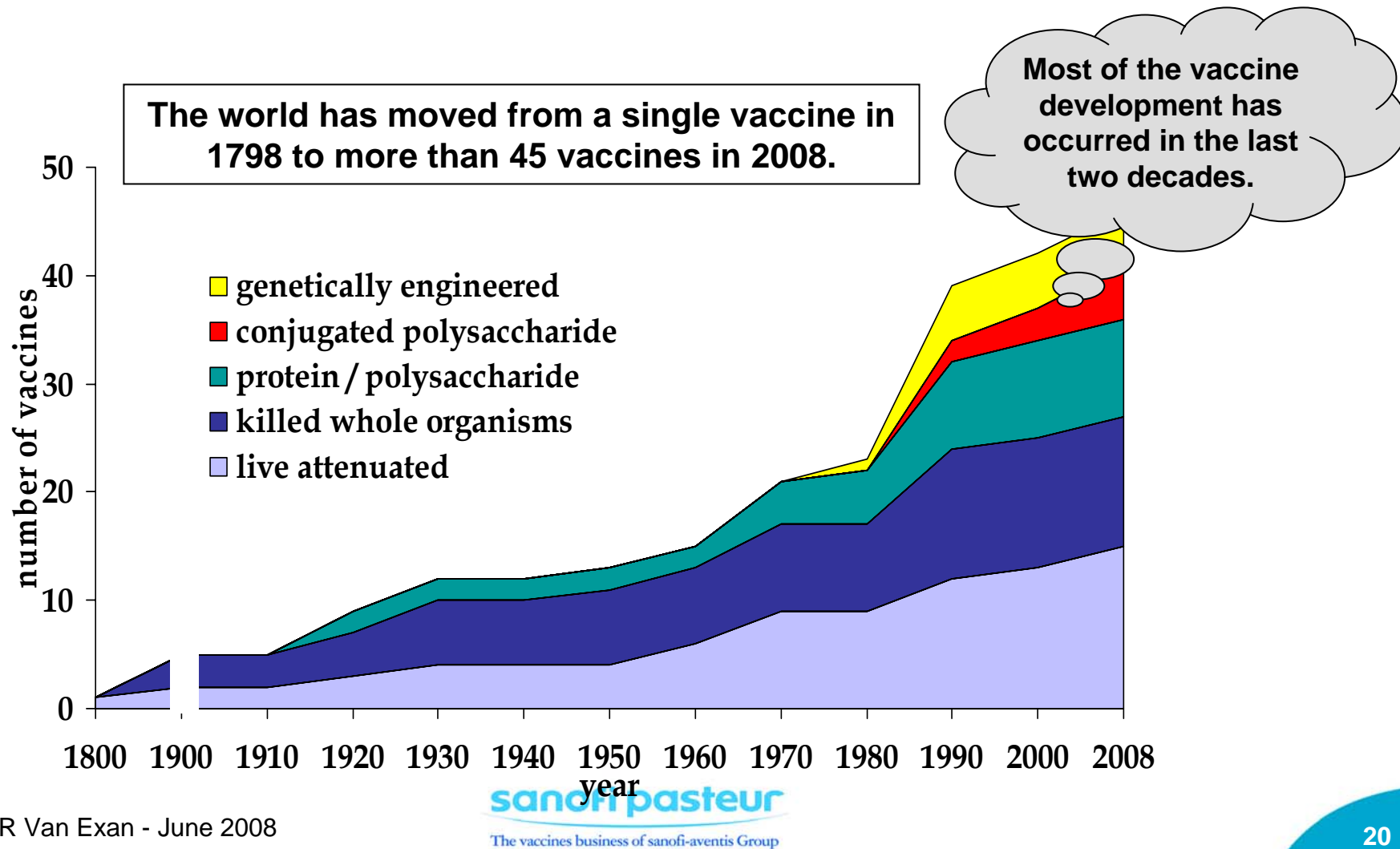


Major Contributions:

- **Eradication of Smallpox**

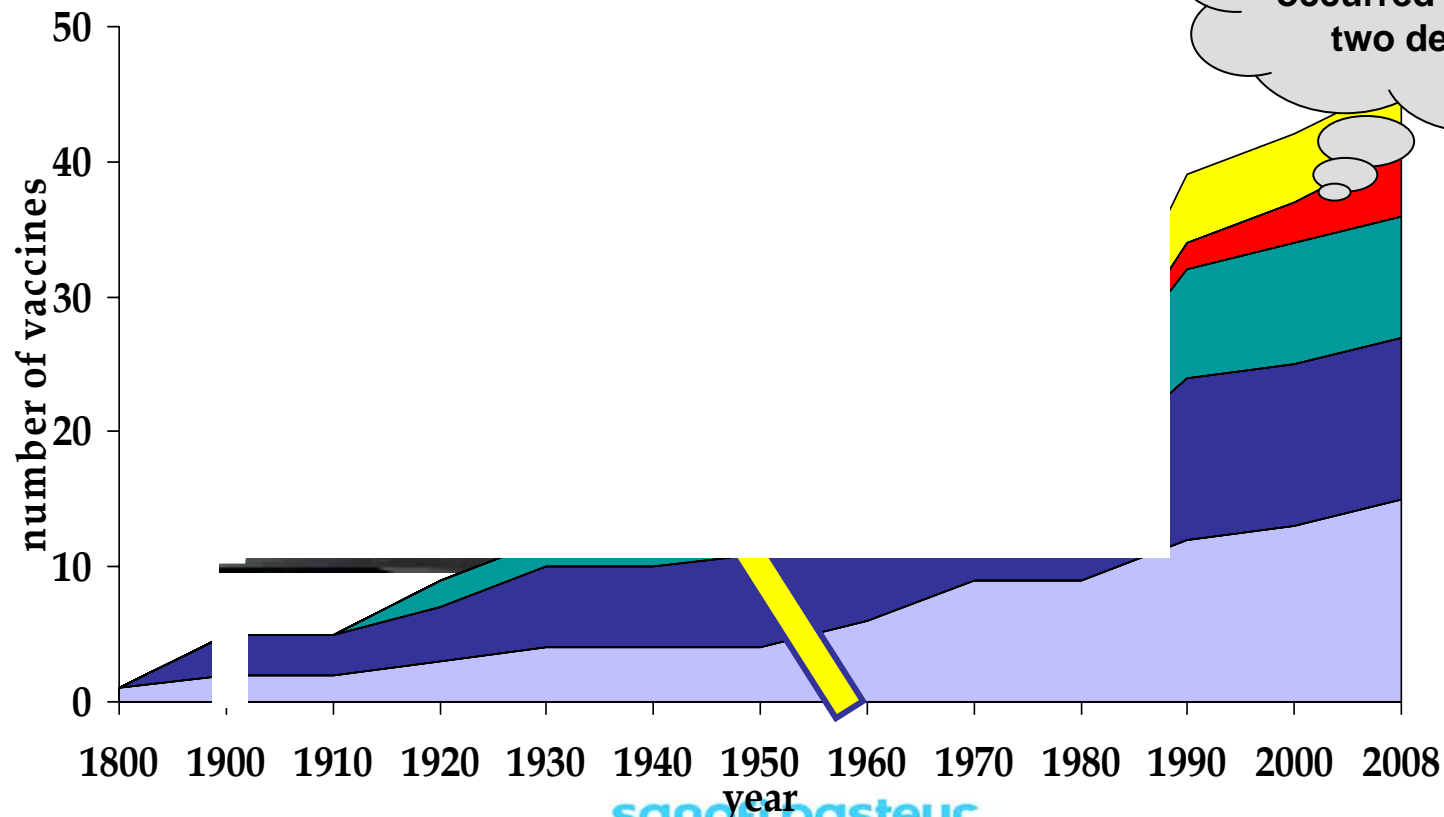


Vaccine Development From the 18th to 21st Century



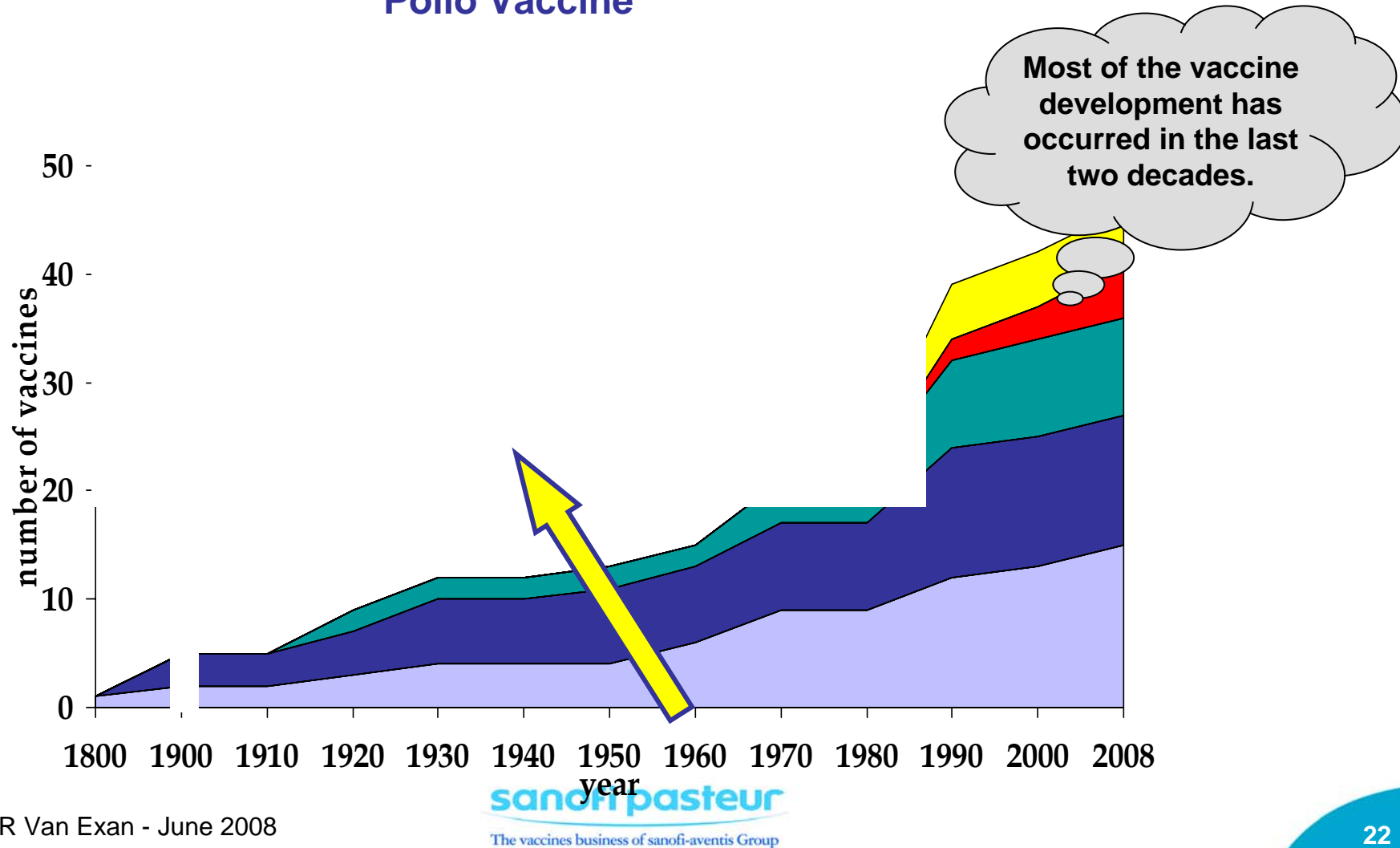
Vaccine Development From the 18th to 21st Century

Polio Vaccine



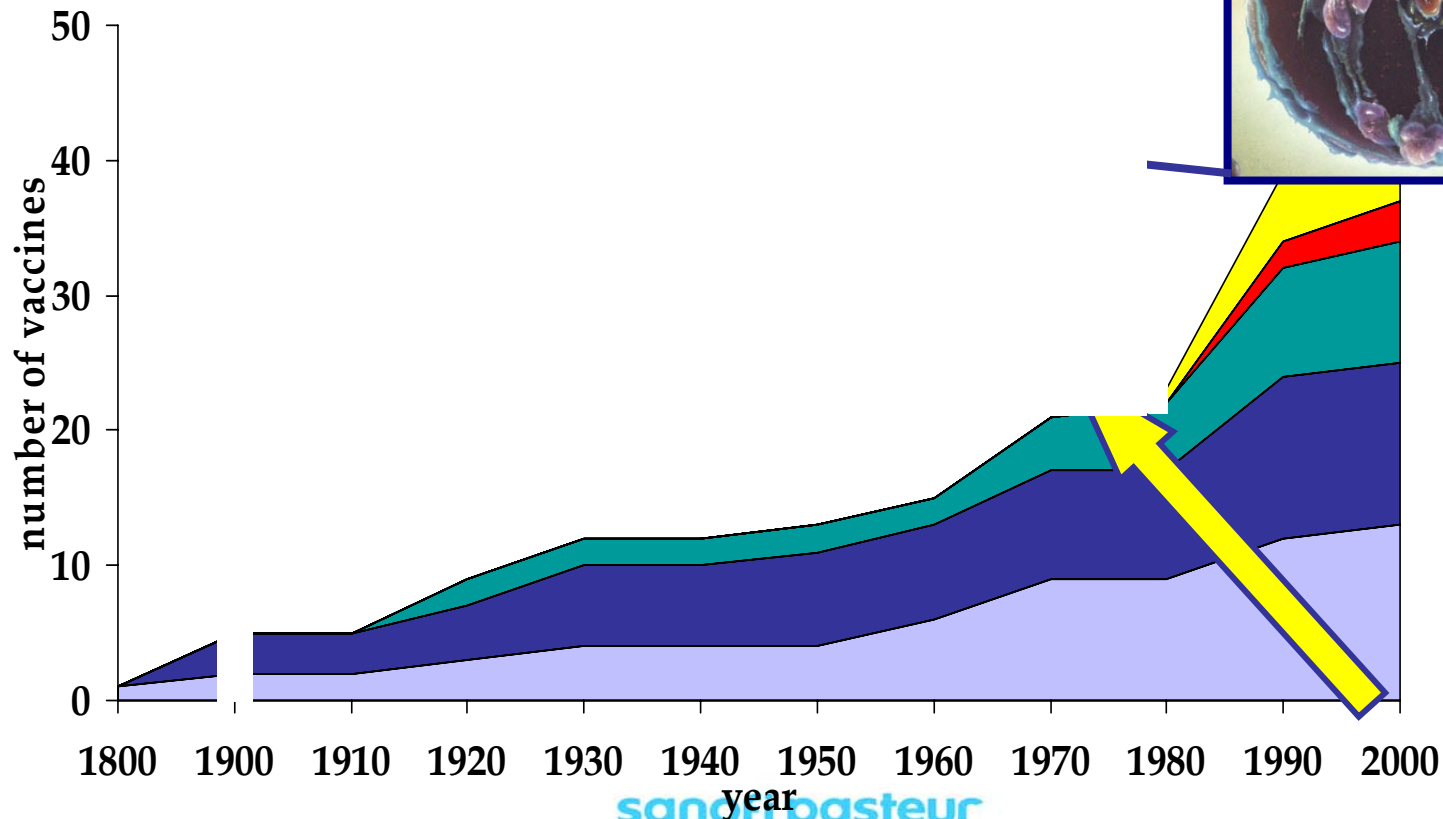
Vaccine Development From the 18th to 21st Century

Polio Vaccine



Vaccine Development From the 18th to 21st Century

Polio Vaccine

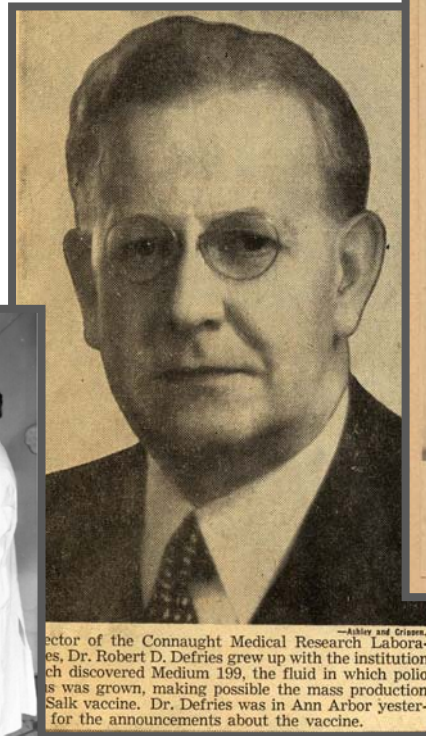
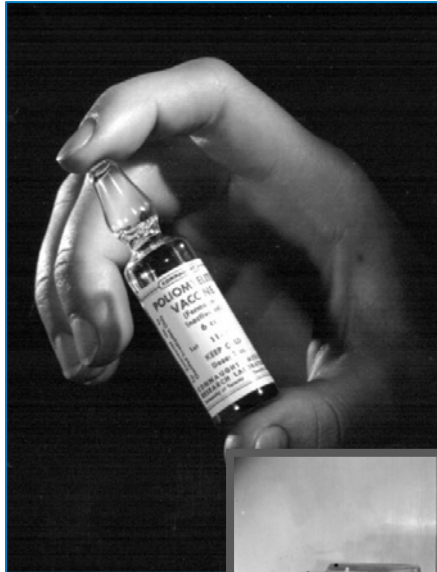


sanofi pasteur Canada Ltd.

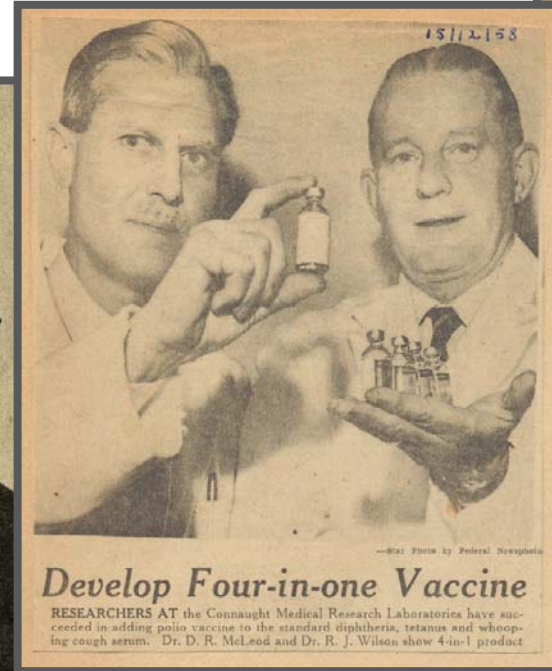


Major Contributions:

● Eradication of Polio



—Ashley and Criswell.
Director of the Connaught Medical Research Laboratories, Dr. Robert D. Defries grew up with the institution which discovered Medium 199, the fluid in which polio is grown, making possible the mass production Salk vaccine. Dr. Defries was in Ann Arbor yesterday for the announcements about the vaccine.



Develop Four-in-one Vaccine

RESEARCHERS AT the Connaught Medical Research Laboratories have succeeded in adding polio vaccine to the standard diphtheria, tetanus and whooping cough serum. Dr. D. R. McLeod and Dr. R. J. Wilson show 4-in-1 product



50 years of polio vaccination in Canada
50 ans de vaccination contre la polio au Canada



Major Contributions:

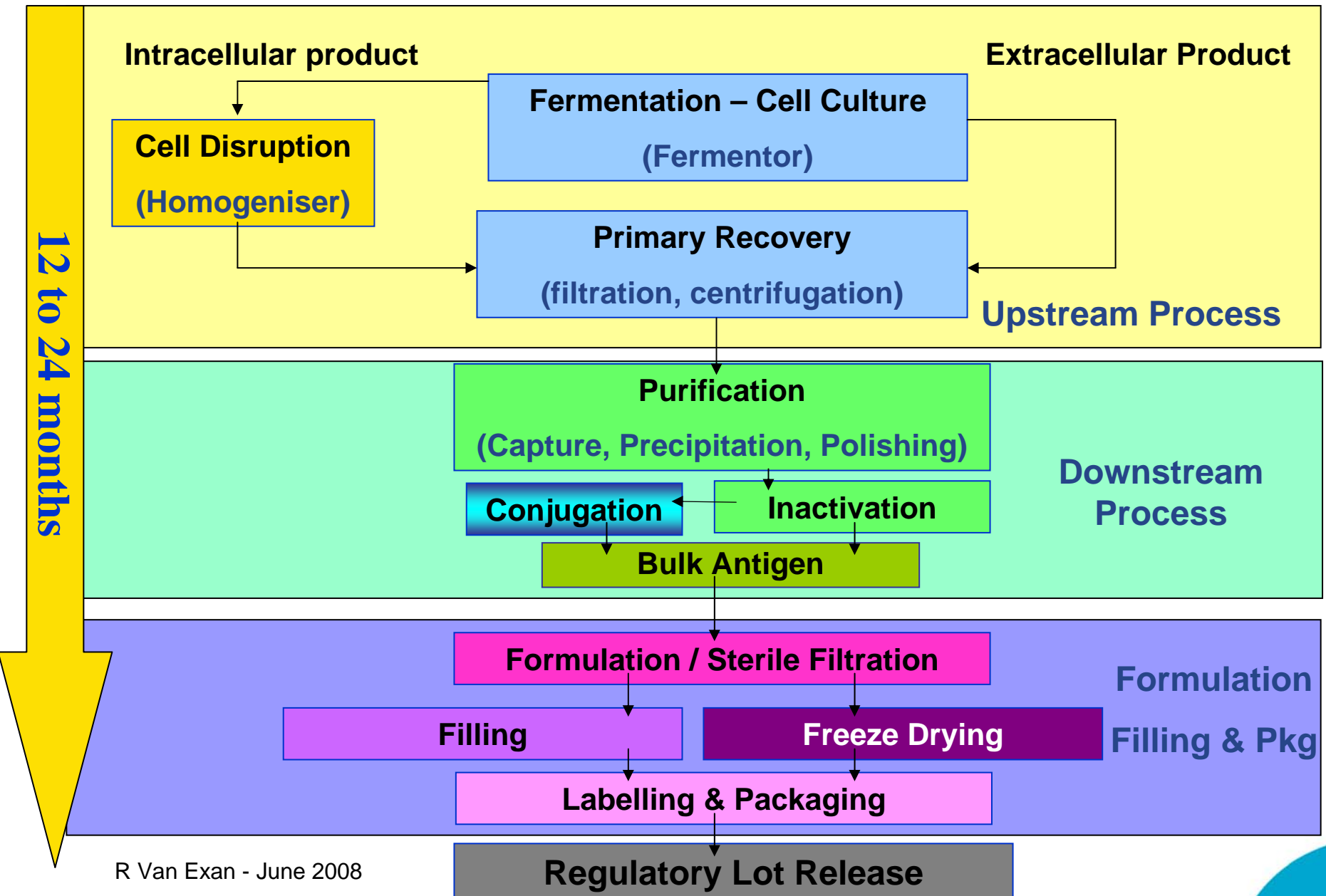
- Eradication of Polio



Vaccine manufacturing – Industrialization



General 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



Downstream Process

Primary Objective:

- removal of impurities
- Maintain biological activity

Secondary Objective:

- Clearance of adventitious agents

Inactivation

- Chemical or physical
- BPL, formaldehyde, heat



Filtration

Formulation

- ❑ Dilution
- ❑ Adjuvant (eg adsorption to AlOH or AlPO_4)
- ❑ 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.



Acellular Pertussis and Combination vaccines

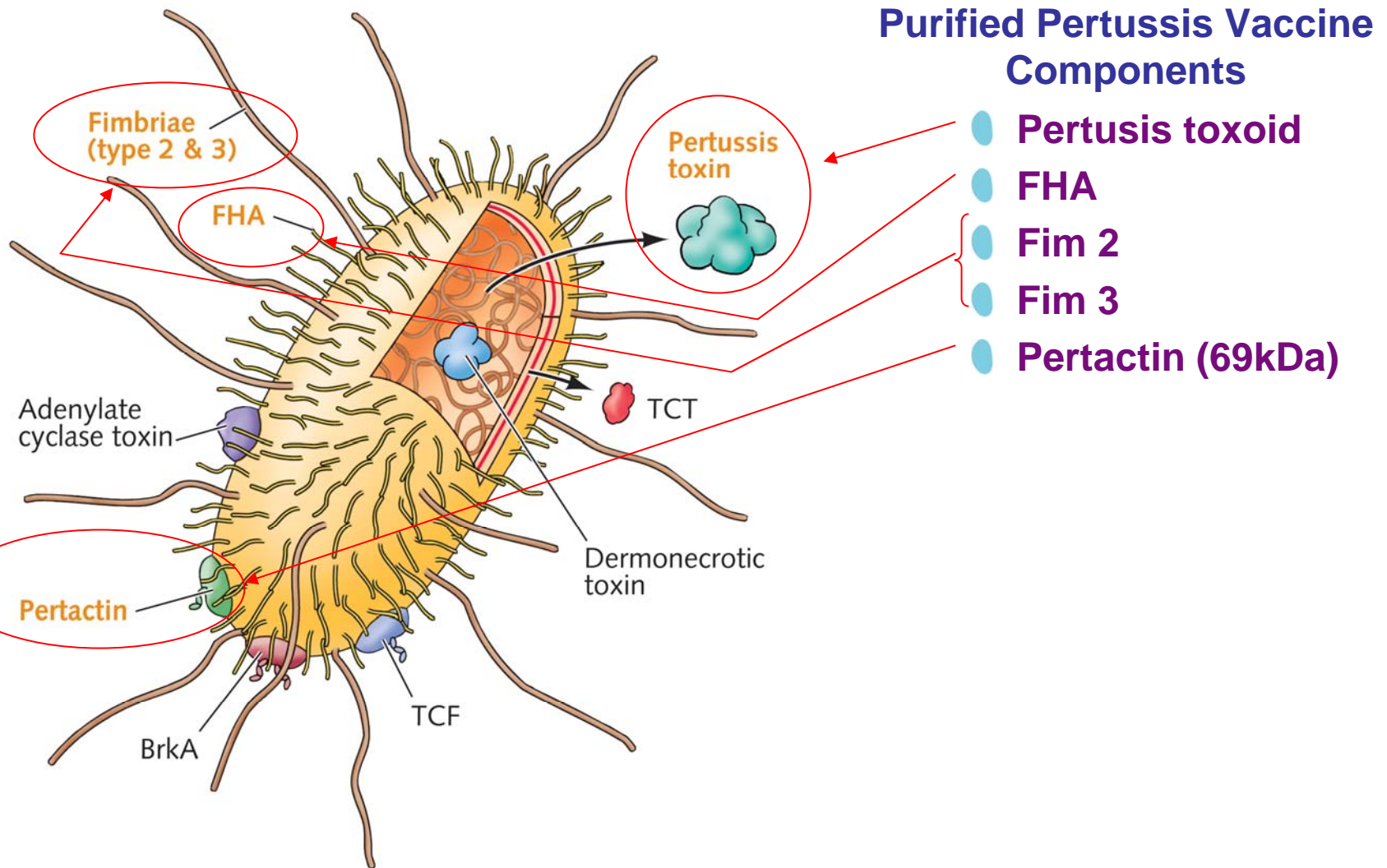
In 1997 sanofi pasteur introduced Pentacel™ an Acellular Pertussis combination Vaccine which contains:

- 5 component acellular pertussis
- Diphtheria
- Tetanus
- IPV
- Hib



The research, development & manufacturing for Pentacel™ combination is completely Canadian

5-Component Pertussis



Manufacturing today - Pentacel



Shortcut to VIDEO_TS.IFO.Ink

Increasing Regulatory Requirements



U.S. Food and Drug Administration

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH



World Health Organization

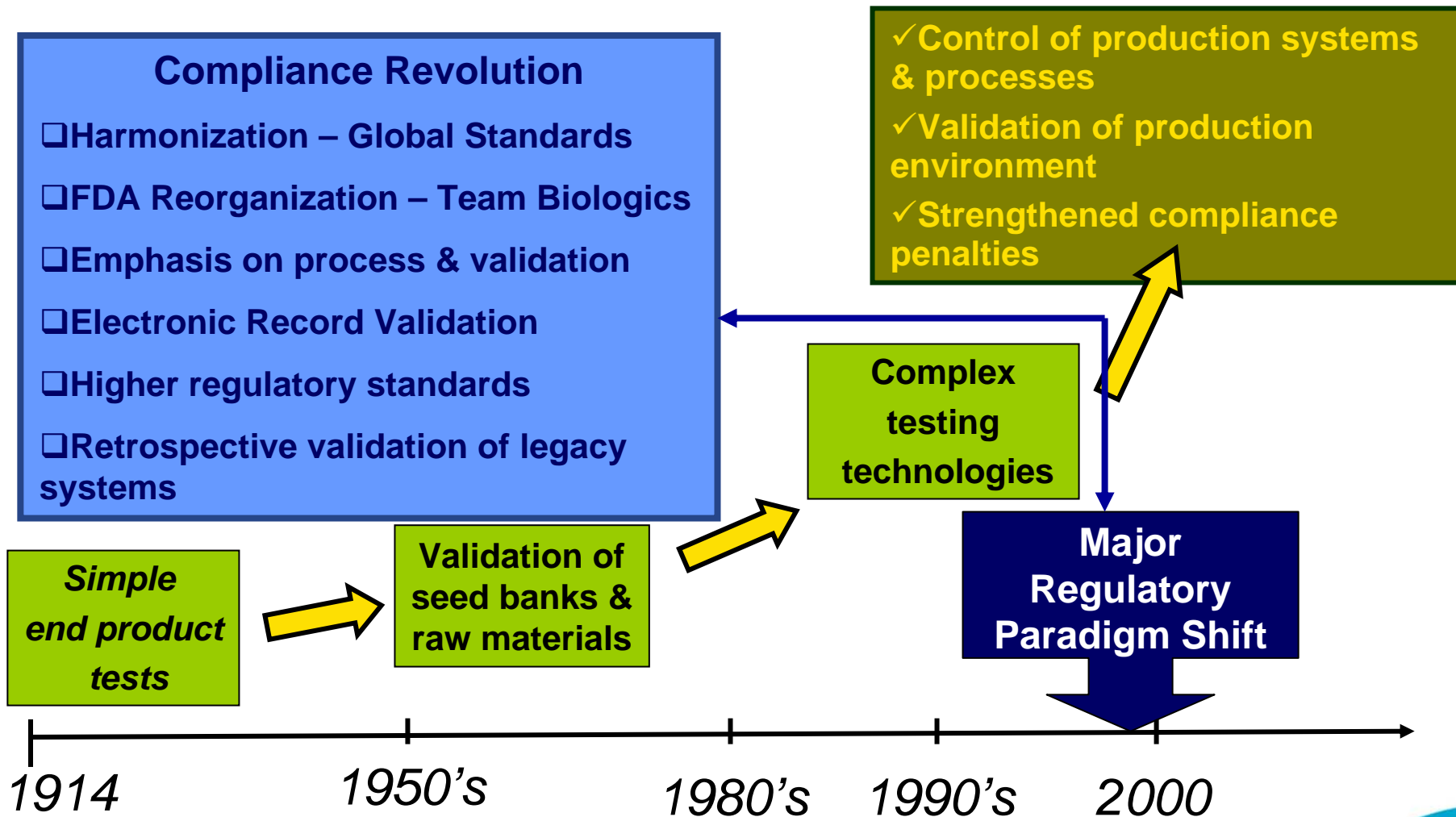


sanofi pasteur

The vaccines business of sanofi-aventis Group

Compliance Revolution

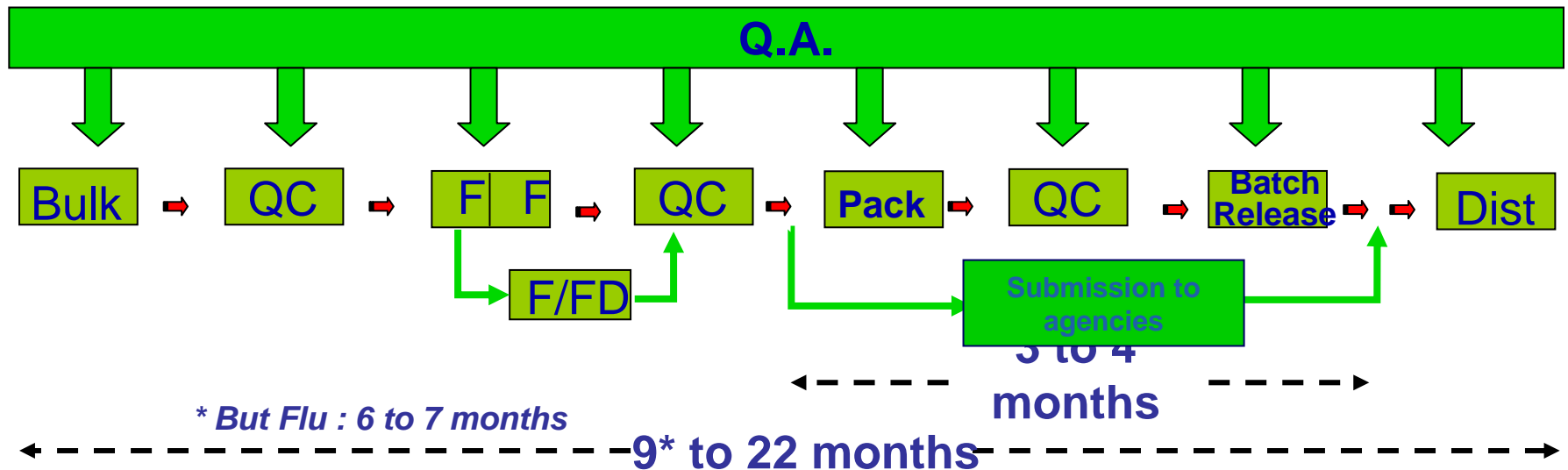
A Paradigm Shift



New concept in cGMP

Now compliance requires:

- ❑ Demonstration of control and reproducibility of all systems and processes throughout the full manufacturing cycle.
- ❑ Dramatic increase in facilities investments, time, data and personnel



Impact of Increasing Regulatory Compliance on the Vaccine Industry

Lot Release

- Testing of every lot by manufacturer and regulator – test discrepancies
- 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

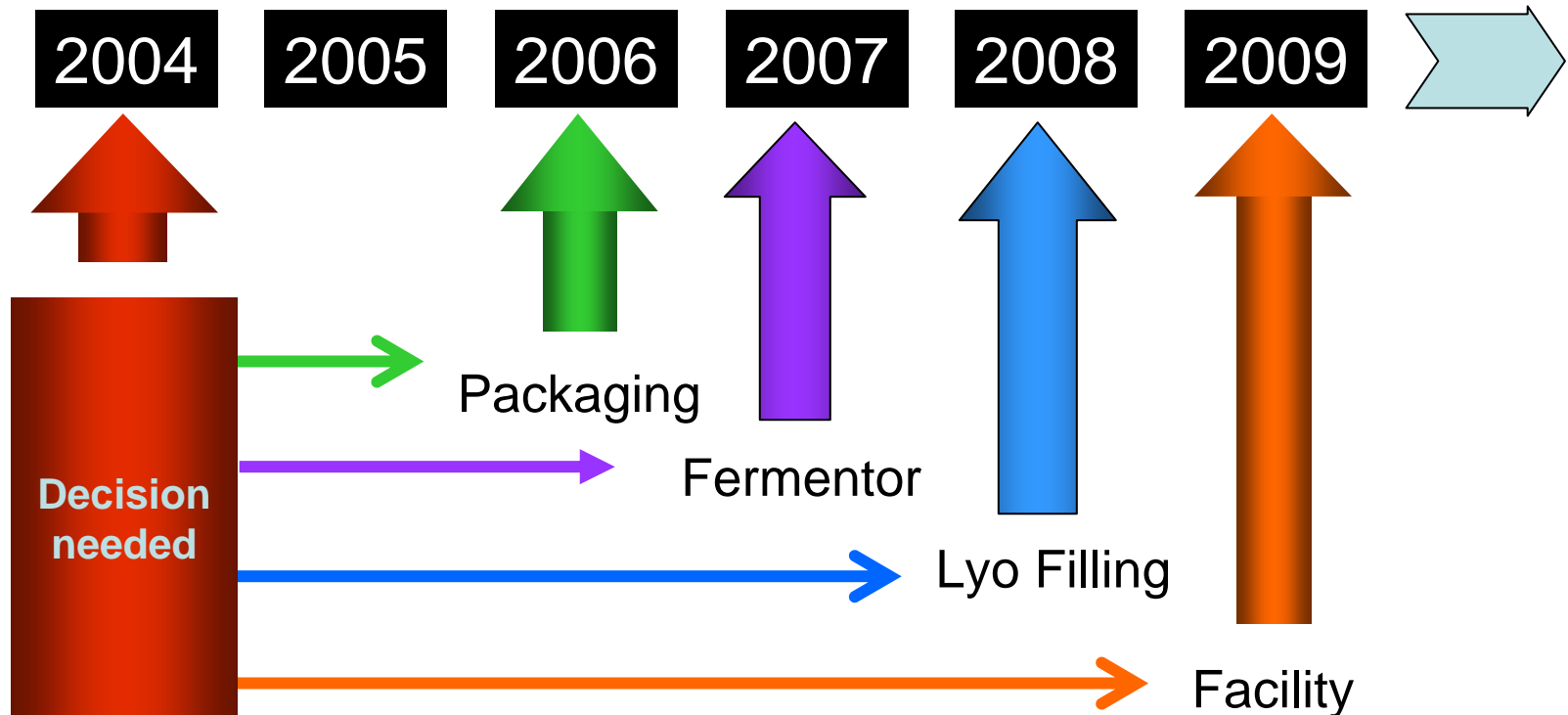
Cold chain disruption

- 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

Timeline for Capacity Increase



Decision timeline for capacity increase

Impact of the Compliance Revolution

Increased Vaccine Production Costs

- Manufacturing Costs
- Quality Control and Quality Assurance Costs
- Manufacturing facility costs

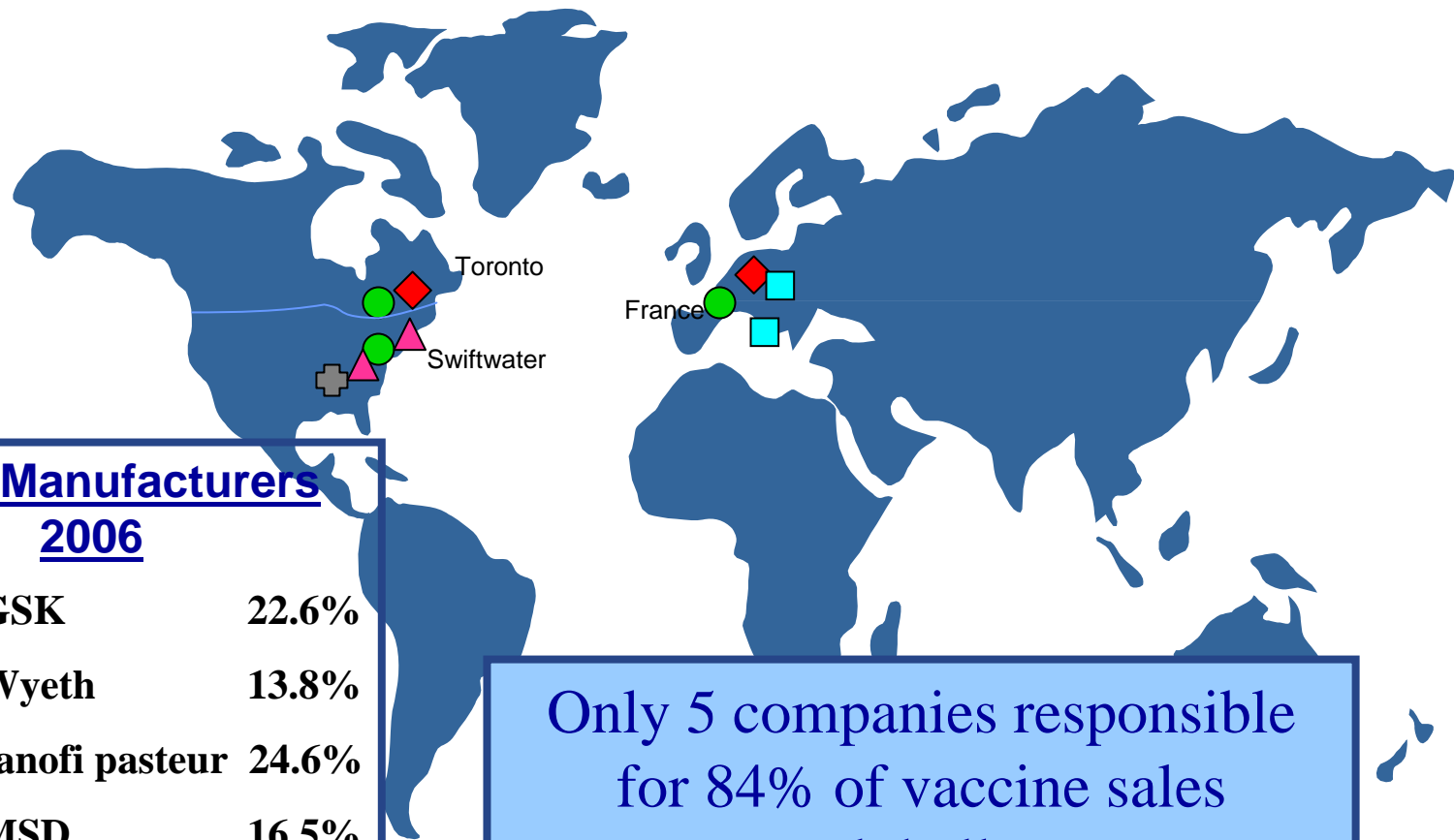
Reduced Capacity

- WIP Losses
- Longer production cycles

Reduced Profitability

- Plant closures
- Companies leaving the industry

Global Vaccine Supply



Top 5 Manufacturers 2006

◆	GSK	22.6%
+	Wyeth	13.8%
●	sanofi pasteur	24.6%
▲	MSD	16.5%
■	Novartis	6.0%

Only 5 companies responsible
for 84% of vaccine sales
globally

Next.....

