Influenza Vaccine Production

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Introduction

- Inactivated Influenza Virus Vaccines
  - Commercially Available for More than 50 Years in USA
    - Parenteral injection
    - Egg vs Tissue Culture

- Live Virus Vaccines
  - In Clinical Development for Commercial Use
    - Intranasal inoculum
Similarities and differences in inactivated influenza virus vaccines

- Comparing Different Years
- Comparing Manufacturers
- Comparing Content
Comparing Different Years
Year to Year Changes in Vaccines

- Influenza vaccines most effective if vaccine viruses match wild viruses
- At least one strain changed in almost every year because of antigenic drift and shift
- Vaccine valency relates to circulating strains
  - Influenza B, Influenza A H1N1, Influenza A H3N2
Strain Change Implications

- Unknown vaccine yield
  - Vaccine output limited by strain with lowest yield
- Unknown impact on vaccine stability
  - Vaccine recall 1996
- Unexpected rare adverse events
  - GBS observed with “swine” flu vaccine
Comparing Manufacturers
Inactivated Vaccine Manufacturers

- Currently 1 manufacturing facility located in USA
  - 3 as recently as 2000
  - As many as 5 (1970’s)
- 15+ manufacturing facilities on 4 continents
- Increasing vaccine demand in USA
  - 20 million doses (1989)
  - 80 million doses (2003)
Vaccines Used in the USA

Sources of vaccine 1990-2003
- Connaught (Aventis Pasteur), Swiftwater, PA, USA
- Evans Vaccines, Liverpool, England
- Wyeth Vaccines, Marietta, PA, USA (ceased 2002)
- Parke-Davis (Parkedale), Rochester, MI (ceased 2000)
Manufacturing Similarities

- Living substrate (eggs)
- Influenza reference viruses for use in vaccine recommended by USPHS (and WHO)
- Purification steps to reduce non-viral (egg) materials and chemicals
- Chemical inactivation
- Sterile but with residual endotoxin
- Preservative
Manufacturing Differences

- Proprietary chicken flocks
- Proprietary seed viruses
- Process differences
  - Sucrose zonal centrifuge vs. chromatography
  - Disrupting agent (detergents and lipid solvents e.g. ether)
Disrupting agents

- Cetyl trimethyl ammonium bromide
- Deoxycholate
- Ether *
- Tri-n-butyl phosphate *
- Triton N 101 *
- Triton X 100 *

(* = Used in vaccines in USA)
Comparing Content
Vaccine Content Similarities

- Hemagglutinins standardized to minimum 15 micrograms per dose

- Limits set for endotoxin
  - 21CFR610.11a

- Limits set for chemical excipients including disrupting agents and inactivating agents
Vaccine Content Differences

- Total Protein Content
- Residual viral proteins
  - (Neuraminidase, nucleoprotein, matrix)
- Endotoxin content
- Formalin vs. beta propiolactone
- Thimerosal content
  - (“Preservative free”)
- Adjuvants
  - (None used in USA)
Changes in inactivated influenza vaccines occur yearly to remain current with circulating viruses.

Manufacturing processes vary, but result in products with relatively similar specifications.

Year to year changes in strains and differences between manufacturers result in variations in content but within defined limits.