Vaccine Regulatory Affairs

Development & Licensing, Quality Issues

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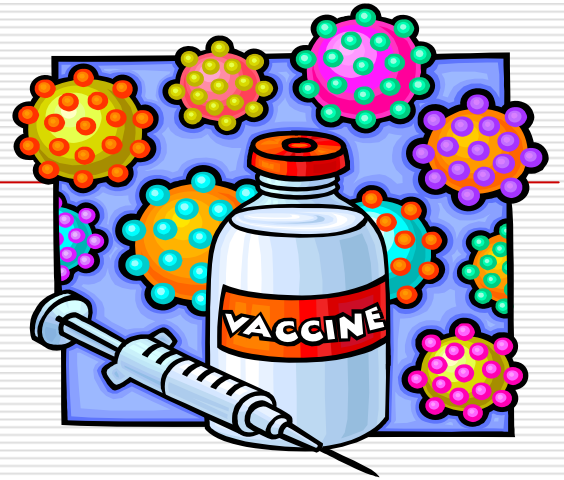
Agenda

- Definition
- History
- Regulation of Vaccines in Canada & trends
- Vaccine challenges
- Vaccine development considerations
- Preclinical & Clinical considerations
- GMP considerations

What is a Vaccine?



Definition

- From Latin ‘vaccinus’, from ‘vacca’, a cow
  - Originally inoculate with virus of cow-pox (vaccinia) to protect against smallpox.
  - Preparation of micro-organisms used as an immunizing agent

Oxford Dictionary

What is a Vaccine?

- "Vaccine – killed or modified live virus, bacteria or ricketttsiae prepared in suspension for inoculation. Used to prevent or treat certain infectious diseases"

  TABERS CYCLOPEDIC MEDICAL DICTIONARY

- Now subunit, recombinant proteins, DNA vaccines
  - Animal cells
  - Insect
  - plant ….

History of Vaccines

- Infectious diseases connection
  - 1796 Smallpox
  - 1885 Rabies
  - 1920's Diphtheria, Tetanus, Pertussis, TB
  - IPV 1950's, combination with DPT approved 1959
  - 1960's OPV, Measles, Mumps, Rubella
  - 1970's Influenza
  - 1980's Meningococcal, Hepatitis B vaccines
  - 1990's Hemophilus b, Acellular pertussis & combinations, Varicella, Hepatitis A
  - 2000 to current: Pneumo & Meningo conjugates, Rotavirus, HPV (anti cervical cancer)

Biological products

- Biological product - any virus, therapeutic serum, toxin, antitoxin or analogous product applicable to the prevention, treatment or cure of disease or injuries of man. (21CFR600.3)

Prophylactic vs Therapeutic Vaccines

- Prophylactic – prevent disease
  - Safety key issue, used in healthy people/children
  - Large numbers needed in clinical studies
  - Public health initiatives, cost/benefit concern
  - General population views- confidence in safety is important

- Therapeutic – to treat disease or chronic condition; to activate or augment the immune system
  - Effectiveness is key
  - Lesser emphasis on numbers & ‘safety’ (risk/benefit)
  - e.g. Cancer (melanoma, prostate, breast, cervix…), HIV

Vaccine Regulation in Canada

- Canadian Food & Drugs Act
  - Part 1, Schedule D
- Canadian Food & Drugs Regulations
  - Part C Drugs
    - Division 1A Establishment licensing
    - Division 2 GMPs
    - Division 4 Biologics
    - Division 5 Clinical trials
    - Division 8 New Drugs

Vaccine Regulation in Canada

- Biologics & Genetic Therapies Directorate (BGTD) of Health Canada
- New Drug Submission requires:
  - Clinical data safety and effectiveness/efficacy
  - Significant manufacturing detail
  - Testing – preclinical, analytical, stability
  - Extensive facility information
- Vaccines subject to On-site inspections, **Lot release**

Vaccine Regulation

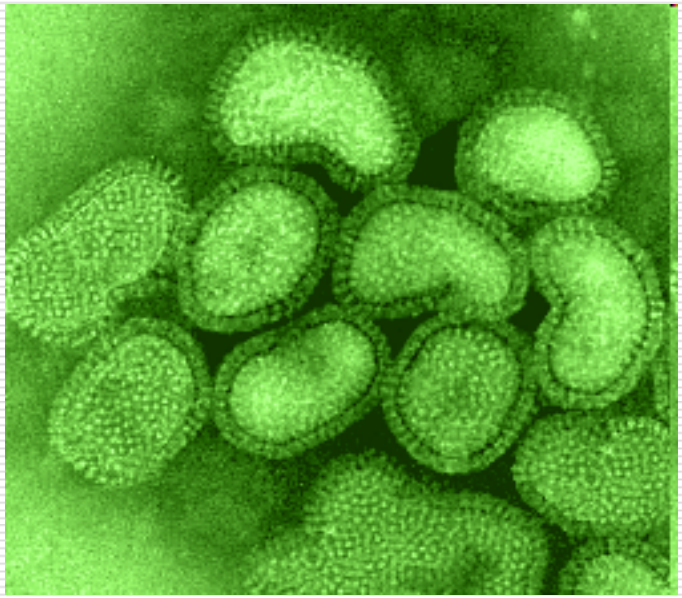
- Factors:
  - Product
  - Testing/characterization
  - Process
  - Facility

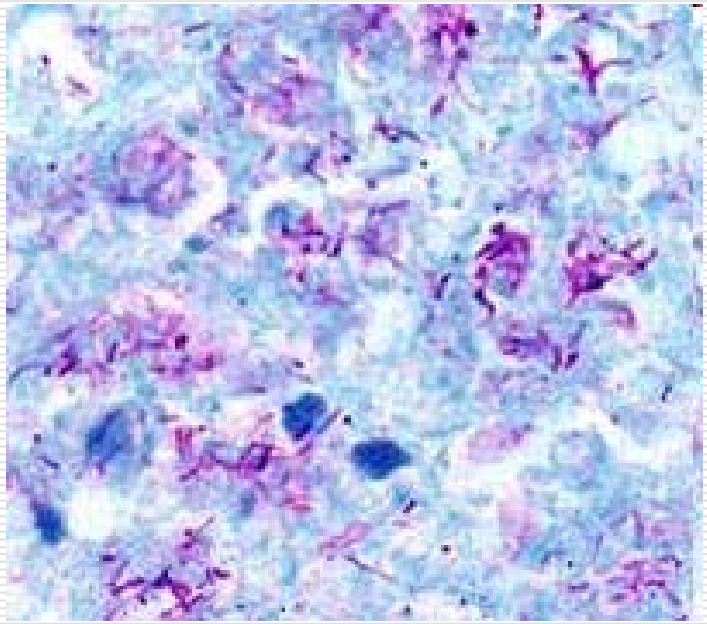
All critical, not just product

Changing Regulation/trends

- Evolving regulations - ICH process
- Events help shape:
  - vaccine shortages,
  - threats (bioterrorism, pandemic)
  - Safety issues - Anti-CD28 Monoclonal Ab
- Public health needs - Meningococcal outbreaks
- Public perceptions of vaccines - thimerosal

Challenges for Vaccines





Challenges for Vaccines

- Biological nature, can't be heat sterilized
- Defined/controlled conditions
  - handle aseptically
  - prevent environmental contamination
- Production process can be long
  - Growth slow
  - Inactivation required, then confirmation
  - Testing can be long e.g. animal potency

Challenges for vaccines – con't

- Robust quality systems required
  - problems can mean no supply for months
- Logistics planning must be detailed & coordinated
  - lot release
  - cold chain maintenance
  - Shelf-life may be limited
  - Cross functional co-ordination important

Vaccine Development

Regulatory issues for development of vaccines

Vaccine Development

Goal:

- Safest possible
- Efficacious
- Least number of doses
- Least amount of antigen (N.B. for infectious diseases with pandemic potential e.g. influenza)

Development Considerations

- Early evidence of safety, effectiveness
- Purity
- Scalability of production process
- Make major changes as early as possible
- Track changes, know why step introduced (development history)

Vaccine Development

- Know the target market
  - Pediatric use
  - Women - need reproductive toxicity
- Keep ‘”Goals” in mind in developing Regulatory & Dev strategy
  - Can the antigen do it all? Adjuvant?
- Keep as simple as possible and focused

Adjuvants – Why use?

- Increase response (Ag poorly immunogenic)
- Promote “broader” response, T cell
- Increase duration of Ab response
- Better protection in particular age group
  - weaker immune systems e.g.elderly & influenza

Adjuvants

- Adjuvants add complexity:
  - Avoid if possible
  - Get data early to show required (preclinical & clinical)
  - Generally response specific to antigen and route of admin used
  - Is there a good animal model to determine type of immune response?
- Adjuvants not licensed by themselves

Regulatory Implications of adjuvants

- Alum (only widely approved adjuv)
- Novel
  - Needs full development
  - Separate tox studies – more preclinical work needed
  - Response specific to antigen & route of admin
  - Understanding of mechanism of action

Preclinical & Clinical considerations

Pre-Clinical Considerations

- Animal models – prediction of human responses?
  - Some good ones exist e.g. ferrets & Influenza
- Any correlates of protection exist?
- Usually 1 species is enough for tox studies, may need to negotiate

Clinical Considerations

- Risk vs benefit very different for preventative vaccines
- More safety required
  - may be given to millions of healthy people: infants → adults
  - less tolerance for adverse effects

Clinical studies

- Phase 1 - Safety
- Phase 2 – Safety, dose response, effectiveness
- Phase 3 – large randomized controlled to demonstrate effectiveness or efficacy + increased safety
  - If vaccine already exists do comparative study (non-inferiority) based on surrogates of protection, e.g. antibody level – influenza, polio

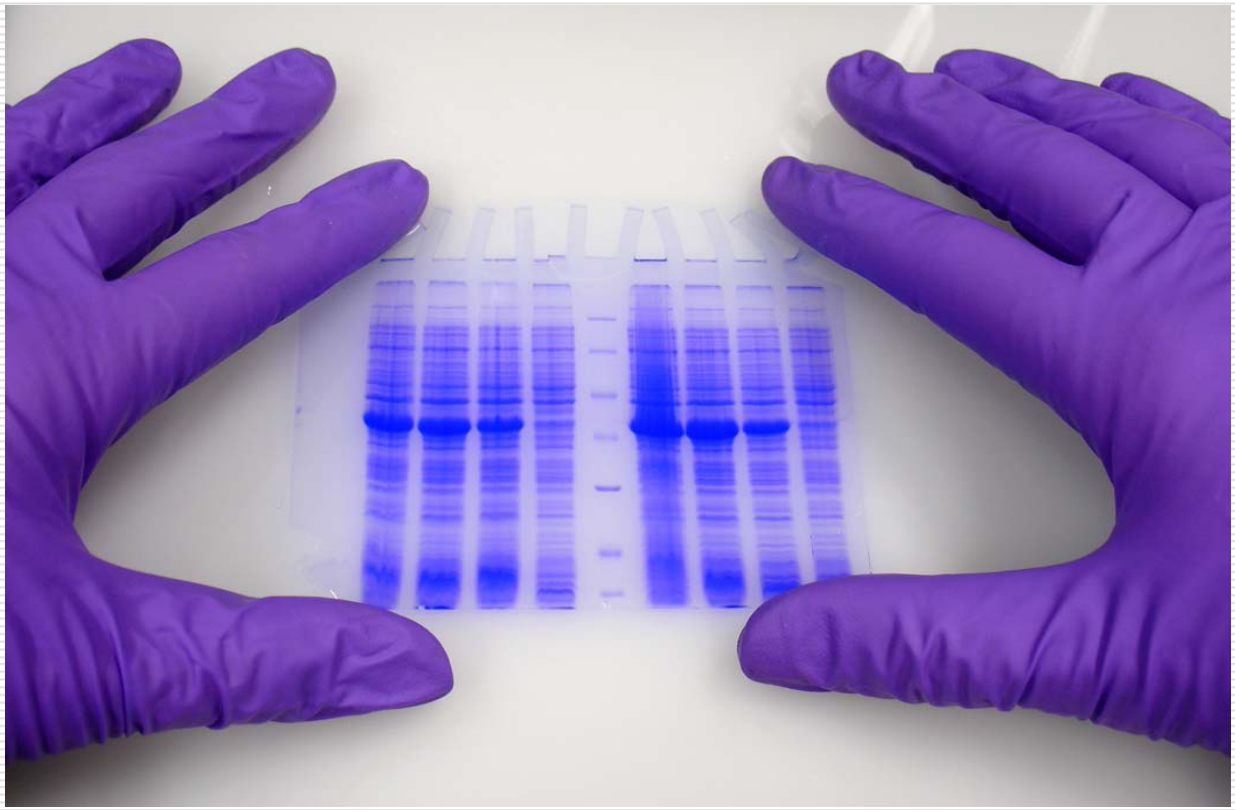
Clinical considerations

- Vaccine Recruitment strategies
  - Sites with large # healthy volunteers
  - Short enrollment
  - Shipping & storage issues to address
- Assure safety, build confidence
  - Public health
  - Regulators
  - Public

Clinical considerations or strategies

- Draft product label early, know the market
  - Age indication?
  - Multiple doses?
  - Concomitant use?
  - How to differentiate product?
    - Benefits may be fewer shots, better safety profile, effective in different age group

GMP Considerations



Biological Raw Materials

- Inherent bioburden (e.g. egg-based, primary cell) of substrates, or
- Biological raw materials like sera, proteins, TSE issues, or
- Easily contaminated (e.g. mammalian cells) substrates
- Infectious (bacterial/viral seed) starting material until inactivated

Characterization – Regulatory items

Know your product!

- What is it?
- How well can you define it?
- Can you make it repeatedly? (Consistency)
- How good is your measuring stick? (assays) Qualified? Specific, sensitive enough?
- Purity & impurity profile?

Quality – Vaccine GMP issues

- Stability
- Potency tests & adjuvants
- Potency & identity of multiple active components
- In-process controls
- Sterility, purity, safety of final product

Document, document, document!!

Quality – Vaccine GMP issues

- Can't be heat sterilized
- Must work aseptically
- Under controlled conditions to ensure SSIPQ
- Often complex, not easily characterized
- Quality systems must be robust

Document! Traceability!

Quality – Vaccine GMP issues

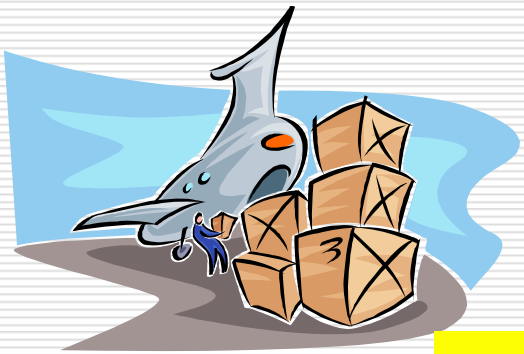
- Documentation
  - SOPs
  - BPR
  - Traceability assured
- Training (GMP & OJT)

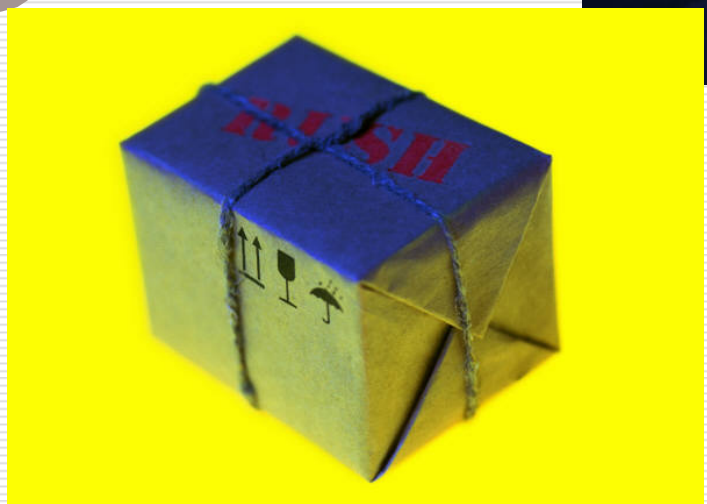
Stability

Data needed:

- Shelf life
- Storage conditions
- Accelerated studies to address Shipping/handling cold chain excursions

Licensed Products Maintenance & Compliance





Post-license Regulatory issues

- Many issues need pre-approval:
  - Labeling changes
  - Manufacturing changes
  - Testing changes
  - Facility changes
- Need coordinated timing for implementation, prevent product shortages, RA plays critical role

Regulatory issues (multiple countries)

- Ensure lots meet specifications in each country
- Coordinate changes to manufacturing, facility or testing & lot releases
- Coordinate labeling changes

Summary

- Vaccines have unique challenges due to their nature
- Most cost effective way to fight infectious diseases
- Immense capacity to improve human health

Thank you!

Questions?