Challenges Inherent in Developing Live Attenuated Bacterial Vaccines

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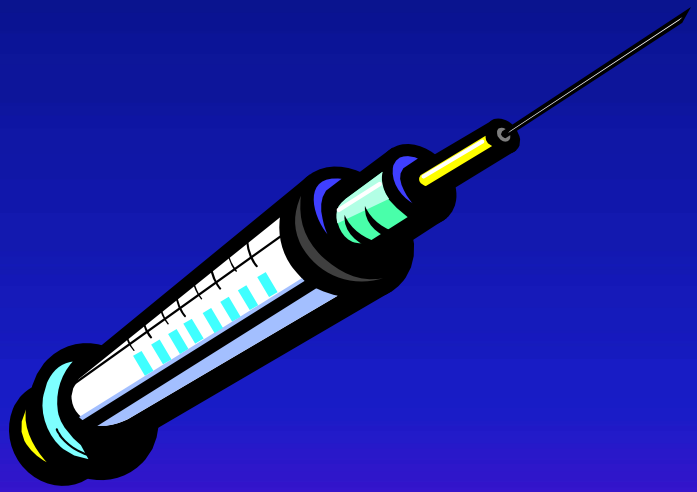

Live Attenuated Vaccines in General

- Many licensed live attenuated viral vaccines (relatively simple genomes)
- Few licensed live attenuated bacterial or parasitic vaccines: *M. bovis* BCG, typhoid Ty21a (relatively complex genomes)
- **But YES, FDA will continue to consider licensing live attenuated vaccines** (cholera, *Shigella*, *Salmonella*, *Francisella* all under IND)

Live Attenuated Bacterial Vaccines: Pro's (and Con's)

- Historically, only live attenuated (not subunit) vaccines have been effective for intracellular bacteria
- Relatively less knowledge base needed to develop (e.g., less information on protective antigens or epitopes, protective mechanisms, adjuvants)
- Potential for superior immunogenicity (cellular) and efficacy

Live Attenuated Bacterial Vaccines: (Pro's and) Con's

- Safety, safety, and safety
- Manufacturing: in process control, consistency of manufacturing
- Testing: may be more complex

Safety Considerations: Mechanism of Attenuation

- Mechanism(s) of attenuation: the more information, the merrier
- Naturally attenuated vs. “rationally” attenuated strains: evaluate potential for reversion to wild type (including recombination in nature)
- Science base, product characterization data may be key

Safety Considerations: Use in Special Populations

- Age related differences in safety outcomes: children, elderly
- Pregnant women, women of childbearing age
- Immunocompromised people

- Different clinical data may be needed to support use in different populations

Safety Considerations: "Escape" Considerations

- Understand potential for shedding by vaccinees, inadvertent transmission to contacts
- Understand survival in environment

- Both product characterization and clinical data may be important

Manufacturing Challenges: A Well Controlled Process

- Potential for contamination with environmental bacteria inherent
- Good environmental monitoring, in-process testing
- Consistency of manufacturing challenging; understanding key features of bacterial gene regulation may be important (e.g., stationary phase, phase variation)

Manufacturing Challenges: Lot Release Testing

- “Sterility” still of interest, but obvious modifications needed
- Modified general safety test
- Identity testing may need to distinguish from virulent form
- Potency testing related to “capacity to effect a given result”

Manufacturing Challenges: Stability Testing

- Viability obviously of interest
- Impact of moisture, if applicable
- Potency testing for stability involves challenges in selecting an appropriate reference standard

Live Attenuated Bacterial Vaccines: The Big Picture

- Total package of product and clinical data should yield an acceptable risk / benefit relationship

- Public acceptance is key, and a moving target