Feasibility of Human Influenza Vaccine Production in Veterinary Vaccine Production Facilities: FDA Issues

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Overview

- Current regulatory mechanisms
- Accelerated approval mechanisms
- Emergency Use Authorization
- Regulatory and technical issues
- Conclusions
Applicable Laws and Regulations: Influenza Virus Vaccine

- Licensed under Section 351(a) of the Public Health Service Act
- Held to provisions of the Federal Food, Drug and Cosmetic Act
- Specific biologics regulations under 21 CFR 600 – 680
- Applicable drug GMP regulations are under 21 CFR 210 & 211
- IND regulations under 21 CFR 312
Review and Licensing Process for Human Vaccine Products

- Complete evaluation of clinical and safety data – for use in targeted population
- Assessment of the manufacturing process
- Review of the manufacturing data
- Review of product testing and CBER testing
- Inspection of manufacturing facility
- After licensure lots are reviewed and released under the lot release program (21 CFR 610.1 and 610.2)
US Licensed Influenza Virus Vaccine Products

- Currently 4 US licensed manufacturers
  - sanofi pasteur Inc., Chiron and GlaxoSmithKline - inactivated split virus vaccines
  - MedImmune - live attenuated vaccine
- Combined total potential capacity (for 2006-7) of approximately 100-120 million doses of trivalent vaccine annually (at 45ug total/dose)
- Current capacity not adequate to meet US pandemic needs, unless antigen needed per dose can be significantly reduced (e.g. adjuvants)
- HHS funding increased capacity (but lag time)
Meeting the Pandemic Flu Vaccine Challenge: FDA Overview and Actions

- Increasing manufacturing diversity and capacity
- Developing needed pathways and regulatory processes to speed vaccine availability – guidance
- Assuring safety and public confidence
- Facilitating vaccine manufacturing/availability
  - current and evolving technologies
  - produce/evaluate H5N1 and other pandemic vaccines
  - antigen sparing advances, adjuvants and delivery
- Pandemic prevention strategies
- Global assistance, cooperation, harmonization
Pathways to Speed Availability: Licensure of Pandemic Vaccines

- FDA views a pandemic strain used in a licensed manufacturing process as a strain change.
  - For licensed manufacturers (inactivated or live vaccine) would not be treated as a new *vaccine* but as a clinical supplement to the application, subject to expedited review:
    - Dosing and immunogenicity, safety if as higher doses.

- Either a wild type or reassortant virus (including reverse genetics) can be used.
Pathways to Speed Availability: Accelerated Approval

- FDA considers there to be a short supply and influenza is a serious and sometimes life-threatening disease
- HI anti-HA antibody levels likely surrogate
- Accelerated approval based on immunogenicity
- GSK data generated/reviewed and approved very rapidly enhancing annual supply and pandemic preparedness - 900 person safety/immunogenicity study planned/reviewed/enrolled in month
Pathways to Speed Availability: Accelerated Approval

- Indicates that with preparation, substantive and needed data can potentially be rapidly obtained even in an evolving pandemic situation.

- We can consider similar approaches for most pandemic vaccines, including adjuvanted, cell and recombinant.
Draft Guidance for Industry

- Two documents issued on March 2, 2006
- Clinical data needed to support licensure of trivalent inactivated influenza vaccines
- Clinical data needed to support licensure of pandemic influenza vaccines
Considerations for Human Vaccine Products for emergency use

- Need to have product available in large quantities in a very short period of time - to be balanced against -

- Use in hundreds of millions of healthy individuals (including children) with limited clinical or manufacturing information
Potential Manufacturing Options in an Emergency

- Increase the capacity of current licensed manufacturers by utilization of other approved manufacturing facilities under contractual arrangements.
- Use of human vaccine products under IND or EUA for which there is some clinical experience supporting safety and immunogenicity but which are not yet licensed.
- Use of veterinary vaccine product facilities to manufacture human flu vaccine products under IND or EUA.
Use of Veterinary Vaccine Manufacturing Facility - Considerations

- Production issues such as the number of doses that could potentially be manufactured
- Need to assess potential issues from the veterinary products manufactured in the facility facility that could impact on human flu vaccine (what host cells being used; adventitious agents)
- Need to assess the impact on veterinary products by bringing human vaccine components into veterinary product facility
- Need to assess the ability to transfer the manufacturing process to the veterinary vaccine facility
Use of Veterinary Vaccine Manufacturing Facility - Considerations

- Need to assess the facility/systems/equipment and the controls in place to manufacture human flu vaccine according to CGMPs
- Need to assess the inactivation of adventitious agents and cleaning of manufacturing areas and equipment
- Potential use of dedicated equipment for human flu vaccine campaigns
Tools to Speed Product Availability and Facilitate Evaluation/Approval

- Early and frequent consultation between sponsor, end user (if different), and FDA
- Fast track
- Priority review
- Accelerated approval – surrogate
- Approval under “Animal Rule”
- Availability for emergency use under IND or Emergency Use Authorization (EUA)
Product Availability under IND

- Facilitated implementation to use products under IND in an emergency (e.g., smallpox or anthrax release)
  - “Streamlined” IND – flexible requirements
  - Informed consent required per regulations
    - Frequently significant uncertainty re: risks/benefits
  - Potentially cumbersome for widespread use
Emergency Use Authorization (EUA):

- Sec. of HHS can declare emergency after Sec. of Defense, Homeland Security, or HHS determines an emergency (or potential for one) exists, affecting national security
- Sec. of HHS (FDA) can authorize use of product:
  - For serious or life-threatening condition
  - No adequate, approved, available alternative
  - Known & potential benefits outweigh known & potential risks
- EUA granted for up to 1 yr: can be renewed
Groundwork is Needed for Broad Emergency Use Under IND or EUA

- Product may be used very widely in multiple populations
- Therefore, should have reasonable evidence of safety and support for efficacy or likely surrogate such as immunogenicity
- Primary time challenge in development is proof of principle and making product consistently - not clinical studies or review
- This should be done before emergency (or pre-pandemic/epidemic) wherever possible
- Managed, prioritized, funded processes needed to identify and develop candidates, assure data will be available to support use in an emergency
Risk/Benefit for Emergency Use Products

- FDA assesses risk/benefit for each product/use and the situation on the ground at that time
  - Treatment: for otherwise untreatable, serious illness, reasonable to tolerate significant risk
  - Prevention: if given to well individuals, balance shifts, especially if pre-exposure (or pre-outbreak)

- Lack of efficacy can be a safety issue
  - Something is not always better than nothing
  - Ineffective therapy can inhibit development of effective therapies

- All such products need objective and effective risk communication
Facility and production concerns for the manufacture of human products in veterinary product facilities

- Potential for the introduction of adventitious agents into human and/or subsequent veterinary products
- Ability to decontaminate facility/equipment after campaigns
- Appropriate systems and controls in place
- Cross-contamination between products
- Technology transfer issues
Communication re: benefit/risks critical
- Includes uncertainty of pandemic/epidemic - as vaccine benefit depends on it
- Likely better in non-crisis or routine situation - priming

Ability and process to reevaluate changing situations

Public's safety concerns and expectations are important and significant (and even more so today) and can affect, and even derail, vaccination plans

Importance of safety monitoring in use

Confidence in vaccines, governments and public health systems will be on the line

“Those who cannot remember the past are condemned to repeat it”
Rapid Flu Vaccine Production

- January: Prepare Seed
- February: Outbreak
- March: Monovalent Production
- April: Fill/Test
- May: First Vaccine to People!
- June: Immunogenicity?
- July: Active Safety/SAE Data/HCD
- August: Continued Pharmacovigilence
- Licensed vs. EUA
Conclusions

- We have made progress to improve vaccine technology and streamline regulatory pathways - BUT- many issues still need to be resolved to successfully deal with a Pandemic Flu crisis
- Many potential options exist and would be considered
- Expansion of capacity and use of facilities that have been licensed for production of human pharmaceutical products, to produce licensed products, is most straightforward approach to augment production in an emergency
- Any product intended for large scale use, even in an emergency and if used as an unlicensed product, will need to have clinical data that support an assessment that benefits are likely to outweigh risks
Conclusions

- FDA regulations allow flexibility to consider the emergency use of veterinary vaccine production facilities, but this would require a careful risk/benefit assessment of any product and manufacturing facilities – and is best accomplished before a pandemic.
- FDA and USDA have and will continue to engage in discussions to determine if any barriers exist, and if so, take steps to address them.
- Continue to work with other regulatory agencies and manufacturers to facilitate Global Pandemic efforts.