Regulatory Challenges to Production of Veterinary Influenza Vaccines in Human Facilities

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Despite of discussing issues apparently beyond the core scope of vaccine manufacturing, in the following presentation there will be no attempt made to discuss general human or avian influenza vaccination issues in depth, rather to address facts and assumptions with real or potential relevance regarding mutual in/acceptability or in/compatibility between two sovereign universes, the regulation of human and veterinary anti influenza vaccines.

Economic considerations more or less are beyond the domain of vaccine regulation, therefore in the presentation economic aspects are only lightly touched.
Renaissance in Human and Veterinary Influenza Vaccine Production

- H5N1 panzootic: unprecedented political, public health and research interest
- Active immunization through vaccination: perceived as main weapon of the pandemic armamentarium
- Huge gap between potential supply and demand: GAP (Global pandemic Action Plan to increase vaccine supply – 2006)

Sub Capacity Level Vaccine Utilization

- Increased production capacity was not accompanied with proportional increase in seasonal influenza vaccine uptake
- Potential sustainability concern for some of the new developing country influenza vaccine manufacturers
- Yearly routine influenza vaccination must be increased globally
- Contract manufacturing of veterinary influenza vaccine?
Task Assumptions

- The actual veterinary product is an oil-emulsified adjuvanted inactivated vaccine propagated on embryonated hen's egg substrate.

- Only upstream processing occurs at the human facility up to the stage of inactivation (inclusive).

- Downstream processing starting with the adjuvantation step is carried out in a veterinary facility.

- The eggs used for the propagation of the veterinary vaccine virus is the same which is used in the facility during human vaccine production.
Concept Development: High-Pathogenicity Avian Influenza Terminology

- Earlier terminologies, such as "fowl plague" and others were replaced by a better defined terminus technicus: the concept of "high-pathogenicity avian influenza (HPAI)" was introduced with it's logical antithesis: "low-pathogenicity avian influenza (LPAI)" at the First International Symposium on Avian Influenza (1981)

- Fine tuning of the above pathogenicity based avian influenza classification system with extending the scope of internationally notifiable avian influenza outbreaks (Office international des épizootis - OIE, 2007) (World Organization for Animal Health)
Original HPAI Versus LPAI Definitions

- An HPAI strain is capable to produce at least 75% mortality within 8 days in 4 to 8 weeks old susceptible chicken after inoculation by IM, IV or intra caudal air sack route, or in another \textit{in vivo} test:

- An HPAI strain has an intravenous pathogenicity index (IVPI) greater than 1.2

- Only H5 and H7 strains were found as high-pathogenic

- All other avian influenza isolates did belong to the low-pathogenicity class (including countless subtype H5 and H7 strains as well)
The original classification dividing high-versus low-pathogenicity avian influenza strains turned to be imperfect as some LPAI strains very easily turned to HPAI even after a single mutation in a particular location of the HA gene.
Improved Pathogenicity Classification with Extension of the Scope of Mandatory Notification of Avian Influenza Outbreaks (OIE, 2007)

- **New entity**: High-pathogenicity notifiable avian influenza (HPNAI), actually it is an extended HPAI group

- HPNAI **also includes** *in vivo* pathogenicity test negative strains if in the *in vitro* test show a specific amino acid sequence pattern at the proteolytic cleavage site of the HA glycoprotein which makes them prone to turn pathogenic in the *in vivo* chicken pathology test too. (Only subtype H5 and H7 strains belong to this class)

- **New entity**: Low-pathogenicity notifiable avian influenza (LPNAI). LPNAI strains are negative in both the in vivo and the in vitro pathogenicity test. (Only subtypes H5 and H7 belong to this class)

- LPAI strains: non-H5 and non-H7 avian influenza strains negative in the *in vivo* pathogenicity test
Selected OIE Requirements for Avian Influenza Vaccines (Terrestrial Manual)

- HPNAI viruses should not be used as the seed virus for production of vaccine
- The need of differentiation of infected from vaccinated animals (DIVA) in vaccinated flocks
- Vaccination alone is not considered the solution to control any subtype of avian influenza vaccine if eradication is the desired result
- Conventional live influenza vaccines are not recommended against any subtype of avian influenza
Requirements for eggs used during manufacture are not uniform for veterinary viral vaccines, i.e. for inactivated influenza the recommendation is the eggs should come from Specific Pathogen Free (SPF) flocks or Specific Antibody Negative (SAN), i.e. good quality eggs. For inactivated Newcastle virus vaccine (NV), "embryonated fowl egg" is the recommendation, for live NV SPF flock is the recommendation.

If HPNA virus is used in challenge studies the facility should meet requirements for Containment Group 4.
Domestic, Regional and Global Influenza Vaccine and Vaccine Strain Banks

- Seasonal adjustment of vaccine composition is not necessary for oil-emulsion adjuvanted inactivated avian influenza vaccines.

- Economically sound stockpiling of influenza vaccines for domestic poultry. Many countries did so when the H5N1 panzootic spread to three continents in 2005/06.

- Thanks to the EU Pan-African Programme for Control of Epizootics and the Canadian International Development Agency an African and a global bank was established in 2006 and 2007, respectively.
Types of Seed Strains in 13 National Avian Influenza Vaccine Banks

- H5 and H7 LPNAI viruses from previous outbreaks in poultry: H5N2, H5N7, H5N9, H7N2 and H7N3
- An H5N1 HPAI virus (!)
- An H5N1 classic reassortant LPAI virus with the HA gene from an H5 wild waterfowl virus
- Reverse genetics derived LPAI viruses: two H5N1 strains and an H5N3 strain (Swayne et al., 2011)
Upstream manufacturing process

- All the preparatory and manufacturing steps must comply without compromise with both the human and the veterinary vaccine regulatory practice of the country.

- The quasi final product of the upstream veterinary vaccine production operation performed at the human facility is the inactivated monovalent virus pool, which represents a pool of single harvests processed at the same time.

- Inactivation is carried out at the monovalent pool level - ASAP (Last step in human facility).
Upstream Manufacturing: Steps Before Virus Propagation

- Control of source material
  - Origin and pedigree of reference vaccine strain
  - Eggs used for seed virus preparation
  - Eggs used for vaccine production
- Establishment and management of master and working seeds
Origin and Pedigree of Vaccine Strain

- Veterinary influenza seed viruses should be well characterized influenza A virus strains with proven low pathogenicity as HPAI viruses should be not used as seed viruses.

- Human influenza vaccines have relatively simple pedigree requirements compared to other human vaccines.

- Since human vaccine facilities have well established cGMP compatible validated change over procedure in place between propagating vaccine strains belonging to different types (A and B) and/or subtype (H1 and H3), introducing another subtype version of the influenza A type virus (H5Nx, H7Nx or H9Nx, etc.) is not unimaginable from regulatory point of view, until veterinary containment requirements were also fulfilled.

- Regardless of the source and route of preparation of a particular vaccine strain the passage history of the parent and reassortant virus strain should be acceptable and approved by both the human and the veterinary authority of the country.
Eggs Used for Seed Preparation

For human influenza vaccine seed virus preparation regulators require the use of embryonated hen’s egg from closed, specific pathogen free (SPF), healthy flocks. This requirement is compatible with the animal vaccine domain as similar requirements are found in OIE guidance documents as well.
Eggs Used in Vaccine Production

- For influenza vaccine production OIE influenza recommendations permits the use of either SPF flock derived hen’s eggs specific antibody negative (SAN) eggs. SAN eggs must stem from well controlled healthy flocks, which monitored by methods approved by local animal health authorities.

- If a manufacturer would entertain the idea to use SAN eggs, it will be very important to make an agreement with regulators early what type of eggs they would consider as eligible for the SAN designation. It is an obvious expectation that chicken flocks established and maintained by new developing country manufacturers are specific influenza antibody free.

- Human vaccine regulators prefer that eggs are coming from flocks which were not vaccinated with live Newcastle disease virus, however, where such practice is mandated by local animal health authorities, the vaccination should take place as early as possible of the chicks lifetime and well before the use of flocks for supply of eggs.
Establishment and management of master and working seeds

- The master and working seed concept for human and avian influenza vaccines are compatible; they are based on similar well tested, time honored principles.

- The established master seed should be controlled and tested for sterility, safety, potency and absence of specific extraneous agents. All the necessary tests approved by the human regulator should be performed, which are in line with the seed control practice of veterinary influenza vaccines.
The Upstream Manufacturing Process

- Virus propagation (inoculation and incubation)
- Harvesting
- Pooling
- Concentration (contrary to human vaccine manufacture it is done only under extraordinary circumstances)
- Inactivation (formaldehyde or beta-propiolacton)
- End of the contract manufacturing process in the human facility (all further processing is carried out at the veterinary site)
Summary -1

- The most important aspect of the procedure is that the live virus manipulation within the human facility must comply without compromise with both human and animal vaccine regulations of the particular country.

- Distinct regulatory bodies falling under the jurisdiction of different ministries of the national governments, National Regulatory Authorities (NRAs) for human vaccines and the so-called competent control authorities for veterinary vaccines.

- Early coordinated involvement of both of these authorities into the planning process is vital.

- Ultimately the manufacturer must obtain the approval of both regulators in addition of the permissions, i.e. biosafety authorities.
The human vaccine facility could not be compromised by the upstream veterinary vaccine production performed there, and *vice versa*, all the requirements set up by the veterinary regulators should meet during operation including the very specific containment requirements in place for the control of laboratory/manufacturing site manipulation of live, highly-pathogenic avian influenza virus strains, i.e. the facility must fulfill the biosafety containment requirement level of the vaccine virus.
Be cautious and realistic!

Choose your target carefully!
Thank you!

Structural Diagram of the Influenza Virus

Back-up slides
Strategies to Control HPAI and LPAI in Domestic Poultry

- Biosecurity measures (bio-containment, quarantine, limiting human contact, movement control)
- Education of poultry handlers
- Rapid diagnosis (culture, molecular) and surveillance
- Stamping out infected flocks with responsible carcass disposal
- Vaccination
International Veterinary Vaccine Use in the Control of Avian Influenza

- HPAI virus target (2002 – 2010): 131 billion doses, 95.5 per cent of them was oil-emulsion adjuvanted inactivated vaccine. Most vaccines (99%) was used by China, Egypt, Indonesia and Vietnam after panzootic H1N1 HPAI became enzootic in domestic poultry.

- LPNAI virus target (2002 – 2010): 10.1 billion doses, 57 per cent of them was oil-emulsion adjuvanted inactivated vaccine.

- LPAI virus target: much smaller scale (10's of millions)

(after Swayne et al., 2011)
Twenty out of the 69 surveyed countries licensed avian influenza vaccines.

All of them required a challenge test for licensure or registration.

This is a potentially limiting factor as according to OIE biosafety guidances if an HPAI virus is to be used in challenge studies, the facility used for the study should meet the required regulatory criteria for handling Containment Group 4 pathogens.

Since the challenge study is performed on the final bulk or the final container in an outside facility this regulatory requirement would be only a concern if an HPAI strain was used as vaccine virus during upstream production.