Stability Evaluation of Vaccines: Lessons Learnt

Teeranart Jivapaisarnpong
ICDRA
2 December 2010
Problems in vaccine stability evaluation

– Difficulties in application of the pharmaceutical accelerated stability testing program to vaccines and the mathematical models used in data analysis. Real time – real condition stability data is mandatory requirement for MA.

– Appropriate testing parameters and frequency of the testing should be selected
WHO Guidelines on Stability evaluation of vaccines

• GL on Stability evaluation of vaccines – adopted in 2006: Principles for different aspects of vaccine evaluation available in the following guidelines:

• Implementation plan:
  – Regional workshops
    • Hosted and co-organized by Korea FDA – April 08
    • other regions 2009-2012
  • IABS workshop – Oct 2008 – CDs available from WHO

• Concept of regional implementation
  – All NRAs and NCLs involved as well as manufacturers (DCVMN, IFPMA, others)
  – Case studies focused on the need in the region in question
  – Opportunity for further developments in specific areas
  – Basis for training curriculum
Key messages

• Guidance: scientific and advisory in nature
• Comprehensive guidance for testing stability
• Guiding principles for evaluation of vaccines for various purposes:
  – Clinical Trial approval
  – Licensing
  – Post-licensing monitoring
• Focus on real time, real storage conditions stability studies instead of relying on thermal stability at lot release
Thermal stability (TS) testing

- TS testing is done as part of lot release for some vaccines especially for live attenuated vaccines to demonstrate the consistency of production.
- Not designed to provide a predictive value of real time
- TS is a shelf-life specification in current WHO vaccine specific recommendations such as OPV, MMR, YF
- For other vaccines: consider relevance of the rate of change for safety and efficacy
- WHO should provide additional tools for evaluating thermal stability data
Stability evaluation at different stage

• Development stage
  – Appropriate stability-indicating parameters as well as potential degradation products that could develop over time should be identified.

• Licensing stage
  – Shelf life (real time stability)
  – Stability profile (Accelerated stability testing)

• Post-licensure stability monitoring
  – to support shelf-life specifications and/or release specifications
  – to refine stability profile of a vaccine in question.
  – identify effect on stability of intentional or unintentional product manufacturing changes.
  – support the conclusion that the vaccine stability profile is still the same as at licensure.
Selection of stability indicating parameters and frequency of testing (1)

- Potential link between biological activity and safety and efficacy demonstrated in clinical trials especially potency assay
- Other parameters indicate changes in vaccine quality with unknown effects on efficacy and safety
  - appearance, pH, antimicrobial agent content, free polysaccharide; desorption from adjuvant, sterility, etc.
Selection of stability indicating parameters and frequency of testing (2)

• Current approach for testing frequency (3, 6, 9, 12, 18 and every 6 months afterwards) described for pharmaceuticals does not apply to all vaccines.

• Appropriate time points for testing depend on vaccine characteristics, the rate of change of the parameter measured, the purpose of testing, study design and subsequent data analysis.
Highly variable assay

• Potency assays based on the *in vivo* challenge test (e.g., Kendrick test for whole cell pertussis and NIH test for rabies vaccine)

• Justification by using each testing result is not appropriate, evaluation by appropriate statistical analysis is needed

• Testing frequency has to be carefully selected.
Analysis of Rabies Stability Studies

In Potency vs. Time (Month)

- Study 1
- Study 2

Calculated and prepared by
Timothy Schofield
Stability of intermediates

• If the intermediates are not processed immediately, proposed storage periods should be validated by suitable stability studies. Real-time/real-condition stability studies are required.

• Stability of intermediate has impact to the shelf life of the finished product.
Stability of Annual Vaccine

• Influenza vaccine: new strains of the virus are introduced yearly. Therefore, limited real-time real-condition stability data are available at time of registration.

• The stability profile of the vaccine with different strains assumed to be similar if the production process is the same. Therefore, the results of the previous real time stability studies of the vaccine with different strains are generally required.

• The results of annual post licensing stability studies are useful information.

• The accelerated study may be useful to estimate the stability profile of the influenza vaccine but the testing parameters and testing frequency should be selected carefully.
Experience with H1N1 2009 pandemic vaccines

- Provisional expiry date of 18 months given to several H1N1 2009 vaccines (based on H5N1 real time stability data) However, accelerated stability profile later shown to be different (data after urgent authorization)
- As a condition of vaccine authorization, manufacturer to perform ongoing stability monitoring to confirm the 18 month shelf life.
- Subsequent potency testing by manufacturers and national control laboratories showed a sooner than expected decline in potency with the result that the expiry date for some vaccines revised to 6 months (eg Australia, Canada)
- No impact on vaccinations already performed but had major impact on vaccine stockpiles.