Available online at www.sciencedirect.com
ScienceDirect
Biologicals 37 (2009) 410–411
IABS BIOLOGICALS
www.elsevier.com/locate/biologicals

An annual vaccine: Seasonal influenza

Teeranart Jivapaisarnpong*, Philip R. Krause

Division of Biological Products, Department of Medical Sciences, 88/7 gr. 4, Soi Bamradnaradoon, Nonthaburi 11000, Thailand

Received 15 July 2009; accepted 6 August 2009

Abstract

The accelerated development process for annual vaccines such as seasonal influenza presents unique challenges for the evaluation of vaccine stability. Real-time real-condition studies provide limited information at the time of registration, while regulators seek evidence that the current vaccine will perform satisfactorily in the field. Participants in the IABS Workshop on Stability Evaluation of Vaccines, a Life Cycle Approach, were offered a case study from the development of the 2007 influenza vaccine. The case study was introduced with preliminary data from the long-term study, as well as results from the completed year long study. The manufacturer also offered a proposed protocol for stability evaluation of vaccines developed in subsequent seasons. Participants were asked to answer a series of questions posed by the regulator, and critique the proposed stability protocol according to the principles described during the workshop.

Keywords: Annual vaccine; Influenza

1. Introduction

The goal of the IABS Workshop on Stability Evaluation of Vaccines: A Life Cycle Approach, was to elucidate designs and analyses that may be utilized to reveal the stability characteristics of vaccines, and through these implement procedures which help assure adequate quality through shelf life of the product. As part of the workshop, participants were tested with several case studies highlighting the unique challenges facing manufacturers and regulators when evaluating vaccine stability. One such challenge is evaluation of an annual vaccine such as seasonal influenza.

A seasonal influenza case study was presented in which new strains of the virus are introduced yearly. Because of the frequent change of process, limited real-time real-condition stability data are available at time of registration. The preliminary data and completed study for a single season were presented, along with a proposed protocol for future changes to the vaccine composition. The participants were asked to address several questions from the regulator. Responses to the questions were discussed among the groups, and key conclusions were highlighted.

2. Case study

The inactivated influenza vaccine contains three strains of influenza virus that generally changes every year. For example, WHO recommended that vaccines in the 2007 season (Southern hemisphere winter) contain the following:

- An A/New Caledonial/20/99(H1N1) – like virus
- An A/Wisconsin/67/2005(H3N2) – like virus
- A B/Malaysia/2506/2004 – like virus.

WHO recommended that vaccines in the 2008 season (Southern hemisphere winter) contain the following:

- An A/Solomon Islands/3/2006(H1N1) – like virus
- An A/Brisbene/10/2007(H3N2) – like virus
- A B/Florida/2006 – like virus.

Due to these changes the influenza vaccine can be used for vaccination only within one year. Therefore, during registration

* Corresponding author. Tel.: +66 296 597 23; fax: +66 259 154 48.
E-mail address: teena@health.moph.go.th (T. Jivapaisarnpong).

1045-1056/09/$36.00
doi:10.1016/j.biologicals.2009.08.001

the real-time real-condition stability study is incomplete. One manufacturer submitted the preliminary results of the real-time real-condition stability study for the inactivated subunit influenza vaccine for registration shown in Table 1. The complete dataset submitted at the end of the year is shown in Table 2.

The manufacturer also proposed to submit the annual stability data for future seasons as follows: three lots of the influenza vaccine produced in that year will be selected for stability study upon storage at 2–8 °C. Each lot will be tested immediately and at 12 months after manufacture for haemagglutinin content, sterility, pH, and description (note: QC test for final lots is test for sterility, pH, description, free formaldehyde, haemagglutinin content, ovalbumin content and endotoxin content).

Table 2
Completed stability results of haemagglutinin contents (μg/ml) of influenza vaccine upon storage at 2–8 °C.

Lot No.	Strain	T0	3 months	6 months	9 months	12 months
A001	A/New Caledonia	32.1	31.9	32.0	33.2	31.1
	A/Wisconsin	31.6	29.4	28.8	25.8	25.2
	B/Malaysia	33.3	29.8	29.1	26.2	28.1
A002	A/New Caledonia	33.7	31.0	29.4	29.9	28.0
	A/Wisconsin	29.9	28.8	26.2	29.1	23.6
	B/Malaysia	30.1	29.8	29.4	29.1	28.5
	A/New Caledonia	32.9	31.9	31.1	30.8	30.3
A003	A/Wisconsin	32.1	32.9	31.7	31.2	30.4
	B/Malaysia	33.9	33.6	29.0	31.7	27.1

Specification on haemagglutinin content: For each strain the haemagglutinin content is not less than 30 μg/mL and lower confidence limit is not less than 24 μg/mL.

3. Workshop exercise

Workshop participants were split into groups of 6- to 8-members per group, and were asked to address the following questions. A workshop facilitator was included in each group to answer questions and to help guide the group through the exercise.

3.1. Questions

1) On registration, is the stability data in Table 1 acceptable for licensing?
2) When the vaccine strains are changed in the next season, is the proposed protocol for an annual stability study acceptable? If not, what should be the appropriate protocol?
3) Is any additional information to the annual study required?

3.2. Discussion (as summarized by Dr. Krause)

The discussion of this case study included recognition of the need to license influenza vaccines based on retrospective stability data, including prior experience with the manufacturer and process. Extrapolation of data beyond real time for influenza vaccines is based in part on the confidence obtained with previous years' vaccines. Participants noted that determination of release requirements by statistical models would require more data than were presented here in Table 1. If the complete dataset presented in Table 2 were available, a separate analysis showed that these data were sufficient to assure that the lower 95% confidence bound at expiry of the worst-case lot would exceed the minimum requirement of 24 μg/ml.

Table 1
Preliminary stability results of haemagglutinin contents (μg/ml) of influenza vaccine upon storage at 2–8 °C.

Lot No.	Strain	T0	3 months	6 months	9 months	12 months
A001	A/New Caledonia	32.1	31.9	32.0		
	A/Wisconsin	31.6	29.4	28.8		
	B/Malaysia	33.3	29.8	29.1		
A002	A/New Caledonia	33.7	31.0			
	A/Wisconsin	29.9	28.8			
	B/Malaysia	30.1	29.8			
A003	A/New Caledonia	32.9				
	A/Wisconsin	32.1				
	B/Malaysia	33.9				

Because influenza antigens change from year to year, and there is the potential for a new antigen to be less stable than previous antigens, it may be appropriate to use historical "worst case" data in assessing new antigens. When previous year's stability data exist for a given antigen, those data will predict the stability of that antigen in a subsequent year, if it is used in a subsequent year's vaccine. Because vaccine needs to be formulated before stability data are available on new antigens, real-time data on influenza antigens play more of a confirmatory role.

Several participants commented that accelerated studies could be valuable in evaluating influenza vaccines. For such studies, one could consider studying vaccine at several temperatures with careful attention to temperature selection to permit prediction of stability relative to long-term stability from previous years and to confirm linearity of degradation. Arrhenius analysis of data obtained from accelerated studies (assuming influenza vaccines followed the Arrhenius model) could also potentially increase confidence in the use of these results to prospectively predict influenza vaccine stability.

Audience members pointed out that long-term real-time stability data are most relevant to the subsequent year's vaccine, but should also be analyzed as it is obtained (suggesting value of additional early data points at 1 and 2 months). The need to obtain data as early as possible also would likely influence the selection of lots for stability testing. It was also suggested that real-time data could include data points beyond 12 months for improved (i.e., more precise) stability estimates. Some participants pointed out that real-time data can also be extrapolated to make predictions regarding vaccine stability even in the current year—although that information may not be available soon enough to influence release titers or dating periods.

Participants also discussed the potential value of studies on intermediates, as well as consideration of testing additional parameters (e.g., endotoxin, stabilizers if they could be degrading, neuraminidase, free formaldehyde). However, the audience concluded that not all parameters need to be evaluated at all times.