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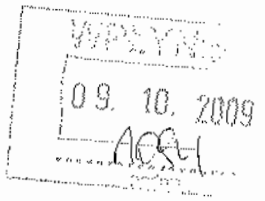
The vaccines division of sanofi-aventis Group



Pani mgr farm. Danuta Parszewska-Knopf
Prezes Rady Zachodniopomorskiej Okręgowej Izby Aptekarskiej
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70-350 Szczecin

EB/54/08

Warszawa, 27 października 2008

Dot. pisma znak ZOIA253/08

Szanowna Pani Prezes,

W związku z Pani pismem z dnia 1.10.2008 r. w załączeniu przesyłamy odpowiedź przekazana przez firmę Sanofi Pasteur S.A., wytwórcę szczepionek we Francji, wraz z jej roboczym tłumaczeniem na jęz. polski.

Z poważaniem

Dr n. farm. Tadeusz Lempke
KIEROWNIK HURTOWNI
Sanofi Pasteur Sp. z o.o.

sanofi pasteur

La division vaccins du Groupe sanofi-aventis.

WEST POMERANIAN PHARMACEUTICAL
CHAMBER
ul. Boleslawa Smialego 4,
70-350 SZCZECIN
POLAND

Marcy l'Etoile, October 22nd 2008

Subject : Thermostability of VAXIGRIP

Vaccines should be kept within +2°C and +8°C and must not be frozen.

In these conditions, vaccines are safe and immunogenic until the expiry date.

Nevertheless, based on stability studies at room temperature, we can say that the efficacy and the safety are maintained for several hours if the vaccine is kept at room temperature (until 25°C).

Regarding Vaxigrip, if the vaccine remains at a temperature of less than 25°C for less than 12 hours, you can used it.

Yours faithfully,

Hélène Priouzeau
Deputy Director Pharmaceutical Affairs Department
Sanofi Pasteur SA

Robocze tłumaczenie na jęz. polski

Zachodniopomorska Izba Aptekarska
ul. Bolesława Śmiałego 4
70-350 Szczecin
Polska

Marcy l'Etoile, 22 października 2008

Dot. termostabilności szczepionki Vaxigrip

Szczepionki należy przechowywać w temperaturze od +2°C do +8°C i nie wolno ich zamrażać.

W takiej temperaturze szczepionki są bezpieczne i immunogenne do upływu daty ważności.

Niemniej jednak na podstawie badań termostabilności wykonanych w temperaturze pokojowej (do 25°C) można stwierdzić, że podczas przechowywania w takiej temperaturze ich skuteczność i bezpieczeństwo są zachowane przez kilka godzin.

W odniesieniu do szczepionki Vaxigrip, można ją stosować w przypadku, gdy pozostawała w temperaturze nie przekraczającej 25°C przez czas nie dłuższy niż 12 godzin.

Z poważaniem

Hélène Priouzeau
Z-ca Dyrektora Działu Farmacji
Sanofi Pasteur SA

SOLVAY PHARMA

Apteki Hurtownie

Warszawa, 20 październik 2008

Szanowni Państwo,

W odpowiedzi na list L.dz. ZOIA 254/08 z 1.10.2008r. informujemy, ze szczepionkę Influvac należy przechowywać w lodówce w temperaturze od 2° C do 8° C, nie można jej zamrażać! Transport powinien odbywać się z zachowaniem zasad "łańcucha chłodniczego" (w opakowaniach termoizolacyjnych z zapewnieniem kontroli temperatury).

Krótkotrwały wzrost temperatury powyżej 8° C (np. w trakcie transportu szczepionki z apteki do punktu szczepień) nie ma wpływu na stabilność szczepionki.

Szczepionka Influvac jest inaktywowaną szczepionką podjednostkową - zawiera wyłącznie antygeny powierzchniowe wirusa grypy (hemaglutyninę i neuraminidazę) w formie glikoprotein. Zalecenie dotyczące jej przechowywania oraz transportu w temperaturze od 2° C do 8° C jest środkiem ostrożności zapobiegającym sytuacji, w której szczepionka podczas transportu (zazwyczaj późnym latem) zostałaby w sposób niekontrolowany wystawiona na działanie promieniowania słonecznego lub podwyższonej temperatury, co mogłoby zniszczyć strukturę glikoprotein.

Firma Solvay Pharmaceuticals dysponuje opublikowanym badaniem*, którego celem było określenie wpływu krótkotrwałego działania podwyższonej temperatury na jakość szczepionki podjednostkowej. Różne serie szczepionki były przechowywane w temperaturze 5° C przez 78 tygodni a następnie w temperaturze 25° C przez czas do 13 tygodni. **Stwierdzono, ze nawet 2-tygodniowe przechowywanie szczepionki w temperaturze pokojowej nie wypłynęło niekorzystnie na jej stabilność.**

Ponieważ incydenty z krótkotrwałą ekspozycją szczepionki na temperatury powyżej przedziału + 2° C do + 8° C podczas jej transportu lub przechowywania zdarzają się we wszystkich krajach, powyższe badanie wykonano, aby potwierdzić przydatność do szczepienia szczepionki wystawionej na krótkotrwałe działanie temperatur powyżej podanego przedziału. W załączeniu cytowana publikacja.

Z wyrazami szacunku

Piotr Truszczyński
Menedżer ds. medycznych

* Stability of influenza sub-unit vaccine, Does a couple of days outside the refrigerator matter? F. Coenen , J.T.B.M., Tolboom, H.W. Frijlink. *Vaccine* 24 *(2006)* 525-531

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Stability of influenza sub-unit vaccine
Does a couple of days outside the refrigerator matter?

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Abstract

In this study 27 full scale production batches of influenza sub-unit vaccine were evaluated on their stability. The batches varied with respect to the strains they contained and regarding the presence of the preservative thiomersal in the solution. The stability study showed that haemagglutinin content was the most sensitive parameter. An increase in the storage temperature strongly increased the degradation rate of haemagglutinin. The degradation rate of the haemagglutinin differed for the different strains tested. However, statistical evaluation of the data obtained for the most sensitive strain tested showed that even exposure during a 2 week period of the vaccine to room temperature would not adversely affect the shelf life claim of the influenza subunit vaccine of 1 year in the refrigerator. Moreover, this study showed that the presence of thiomersal in the solution has no effect on the stability of the vaccine.

Keywords: Influenza vaccine; Stability; Thiomersal

1. Introduction

Influenza is a major cause of morbidity and mortality, affecting all ages and about 20% of the population worldwide. Serious complications can occur in the elderly and individuals at high risk such as patients suffering from chronic pulmonary or cardiovascular diseases, immune suppressed patients or diabetics [1]. These groups are the target for routine annual vaccination for the prevention of influenza.

The influenza virus is constantly changing; therefore the composition of the influenza vaccines changes from year to year to maintain protection for the individuals revaccinated each year. The composition of the vaccine is based on the recommendations by the World Health Organization on influenza vaccines for use in a particular season in a particular hemisphere.

Regular stability testing of the vaccine in its primary packaging is performed on all full-scale production batches of the new vaccine compositions to support regulatory filing and for GMP compliance. To determine the stability of the batches several parameters are investigated, e.g. appearance, pH, content of haemagglutinin antigen, content of thiomersal if applicable, extractable volume and appearance. The result of the most sensitive parameter in the least stable batch determines the shelf-life of the drug product. In general the haemagglutinin antigen content is the most sensitive parameter; however other parameters that could be influenced by storage are tested as well. This publication focuses only on the haemagglutinin content since for all batches investigated all other parameters met the preset requirements and did not provide any additional information regarding the stability of the tested batches. The batches tested in this study were all full scale production batches.

Stability studies are generally performed following the ICH guidelines [2,3]. The purpose of stability testing is to provide information on the quality of a drug product during

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Table 1
Recommended storage conditions for drug products intended for storage in a refrigerator

	Storage condition
Long term stability	5 ± 3 °C
Accelerated stability	25 ± 2 °C/60% RH ± 5% RH

storage at a certain condition. The storage conditions for a drug product intended for storage in a refrigerator are summarized in Table 1 [2].

Testing of batches at an elevated temperature (25 ± 2 °C) is conducted to address the effect of short term excursions outside the proposed label storage condition. Studies under stress conditions may be useful in determining whether (short term) accidental exposures to undesired conditions (e.g. during transport) are deleterious to the quality of the product and also for evaluating which specific test parameter may be the best indicator for product stability [3].

Therefore, it is necessary to simulate non-isothermal ambient conditions with isothermal conditions which can be done by taking the mean kinetic temperature [4–6].

The storage condition 25 ± 2 °C/60% relative humidity (RH) ± 5% reflects climate zone II as part of the split up of the world in four different climate zones. The 25 ± 2 °C/60% RH ± 5% RH has been calculated as the mean kinetic temperature of climate zone II. The temperature pattern in climate zone II is summarized in Table 2 [5].

The permissible extreme temperatures are still covered by the storage condition for climate zone II. For instance 3 weeks exposure of the product at 25 °C is equal to an exposure for 1.8 day at 31 °C/32 °C + 0.5 day at 36 °C.

The relative humidity for the accelerated condition 25 ± 2 °C/60% RH ± 5% RH will not be discussed further because this is not relevant for a vaccine solution that is stored in a humidity-protecting container.

The aim of this study was to investigate what the effect of short term exposure of the vaccine to higher temperatures would be on the quality of the product and its shelf-life. A second objective in this study was to compare the stability of an influenza vaccine formulation containing the preservative thiomersal with that of a thiomersal-free formulation.

2. Materials and methods

2.1. Composition of the influenza vaccine

Table 3 gives the different compositions of the influenza vaccine that were used for the northern hemisphere during the last 4 years.

2.2. Primary packaging of the influenza vaccine

The influenza vaccine is packed in Readyfill® syringes. Fig. 1 shows a schematic presentation of this type of syringe. During storage the vaccine-containing solution is in contact with the glass barrel (glass type HK1) and with the rubber stopper and rubber plunger (both consisting of FM257 type rubber).

2.3. Analytical methods

Influenza vaccine (surface antigen, inactivated) is described as a colorless clear liquid. The haemagglutinin content was determined by Single Radial Immuno Diffusion test [7].

The thiomersal content was determined by ultraviolet spectrophotometry at 473 nm.

2.4. Outline of the stability study and the comparative study of thiomersal-containing and thiomersal-free vaccine

The different influenza vaccine batches were stored at 5 °C/ambient humidity for up to 78 weeks and at 25 °C/60% RH for up to 13 weeks. At regular time intervals samples were taken and the whole set of quality-indicating parameters were tested. Since the haemagglutinin content is the

Table 2
Annual temperature pattern and extreme temperatures in climate zone II

Annual temperature pattern	Mean kinetic temperature	Storage temperature	Permissible extreme temperatures covered per year
21 °C/6 months	25.1 °C	25 °C	36 °C/10 days
26 °C/4 months			32 °C/15 days
30 °C/2 months			31 °C/20 days

Table 3
The composition of the influenza vaccine in micrograms haemagglutinin per dose

Influenza strain	Season 2000/2001	Season 2001/2002	Season 2002/2003[a]
A/Moscow/10/99 (H_3N_2)-like (A/Panama/2007/99 RESVIR-17 reass.)	15	15	15
A/New Caledonia/20/99 (H_1N_1)-like (A/New Caledonia/20/99 IVR-116 reass.)	15	15	15
B/Beijing/184/93-like (B/Yamanashi/166/98)	15		
B/Sichuan/379/99-like (B/Guangdong/120/00)		15	
B/Hong Kong/330/2001-like (B/Shangdong/7/97)			15

[a] *Note*: The same composition was recommended for the season 2003/2004.

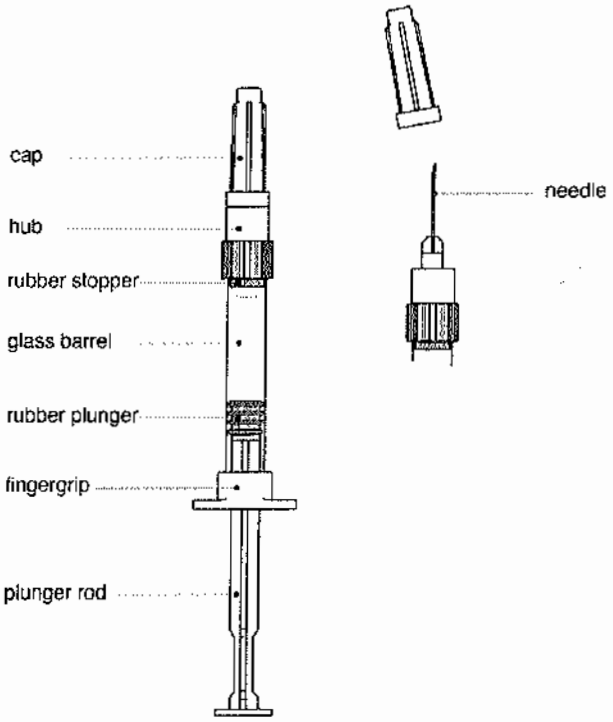

Fig. 1. Schematic presentation of Readyfill® syringe used as primary packaging material.

stability-indicating parameter and the effect of the presence of thiomersal was another item investigated in this study, only the haemagglutinin content and the thiomersal content are reported in this paper.

The shelf-life specifications for haemagglutinin content are: a lower confidence limit ($p = 0.95$) ≥ 24.0 μg/ml, confidence interval ($p = 0.95$) within 80–125% of estimated content. The shelf-life specification of thiomersal was 85–115 μg/ml.

2.5. Statistical methods

The statistical analysis consists of three parts. In part 1 the batches contain thiomersal and are measured during several seasons. For these batches several factors are tested for their correlation with HA content. In detail, an analysis-of-variance of HA content is calculated with week depending on storage condition as co-variables and season and batch within season as explanatory factors together with their interactions with week. Statistically not-significant co-variables and factors will be excluded in order to get a simple statistical model.

In part 2, three batches with and three batches without thiomersal are measured in a single season. The factors correlated with HA content are derived from an analysis-of-variance with week depending on storage condition as co-variables and thiomersal use and batch within thiomersal use as explanatory factors together with their interactions with week. Again statistically not-significant co-variables and factors will be excluded. The difference between the mean initial content of the thiomersal-containing batches and of the thiomersal-free batches is tested against the variation in initial content between batches, and similarly for the difference between the mean degradation rates.

In the last part the degradation rate is determined using linear regression with initial content depending on batch and degradation rate depending on storage condition. When a batch is stored at 25 °C/60% RH for part of the year, we assume that during that part of the year the degradation rate at 25 °C/60% RH is applicable and during the rest of the year the degradation rate at 5 °C. With this assumption we can calculate how many weeks at 25 °C/60% RH result in a guaranteed shelf life of exactly 1 year with the same regression model as before. This guaranteed shelf life with a 95% confidence level equals the lower bound of the 90% confidence intervals calculated with Fieller's method [8]. For the storage condition 25 °C/60% RH the linearity of the degradation is tested by expanding the statistical model with a quadratic week effect for 25 °C/60% RH. If statistically significant, the guaranteed shelf life of exactly 1 year is derived from the degradation rate at week = 0 in the quadratic model.

3. Results and discussion

3.1. The results of the stability study

Before the question can be addressed how much faster the Influenza vaccine degrades at 25 °C/65% RH compared to 5 °C, we need an explanatory model for the data. Such a model will also show the effect of thiomersal on degradation.

In part 1, all batches contain thiomersal and are measured during more than one season. In part 2, three batches with and three batches without thiomersal are measured in a single season.

After ruling out higher order interactions the initial model for part 1 is linear regression of content on weeks where the linear regression may depend on storage condition, season or batch. No statistically significant differences in degradation rate between seasons or batches were found for any strain. However, the mean levels at week = 0 show clear differences between seasons and batches. These differences are tested against the unexplained variation in HA content. For season this is not a correct comparison, since different batches are used in each season. Therefore, the differences between seasons have also been compared against the differences between batches within season. The analysis-of-variance results show that the differences between seasons are not statistically significantly larger than the differences between batches, or in other words are just a manifestation of the differences between batches.

To investigate the effect of thiomersal for part 2 the same approach has been used with thiomersal use instead of season. Since no statistically significant differences between thiomersal-containing and -free batches were found either

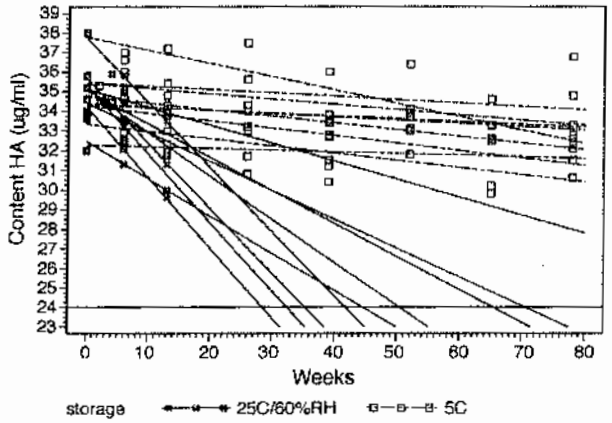

Fig. 2. Regression lines of haemagglutinin content on weeks per storage condition for each season and batch for A/New Caledonia.

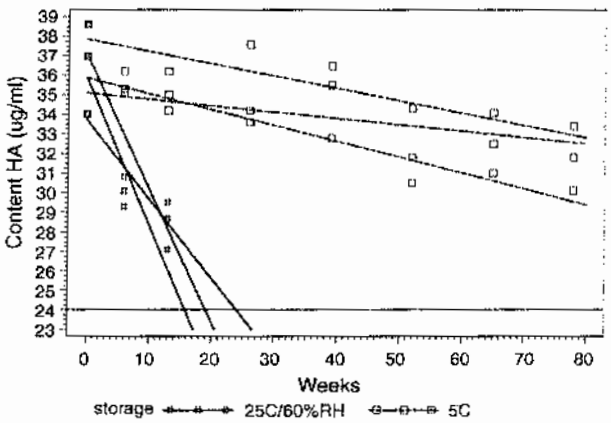

Fig. 4. Regression lines of haemagglutinin content on weeks per storage condition for each season and batch for B/Guangdong.

in initial content or in degradation rate, these factors were not included in the final statistical model.

The above implies that linear regression with an initial content depending on batch and degradation rate depending on storage condition is an adequate model. With this model the mean content per batch at week = 0 and the degradation rate (μg/ml/week) per storage condition were estimated.

The degradation of haemagglutinin of the various strains in the different batches at the two different storage conditions is presented in Figs. 2–6. With the exception of one batch A/Panama all batches met the shelf-life requirements after storage for 78 weeks at 5 °C. The lines given in the figures are the linear regression lines fitted for the different batches. The slope of the lines is a direct measure of the rate of degradation of a certain batch at a certain condition. The degradation at 25 °C is much faster, which is reflected in the much steeper slope for the batches stored at 25 °C. Since a rather large number of batches have been investigated in this study, statistics can be applied to calculate the mean rate of

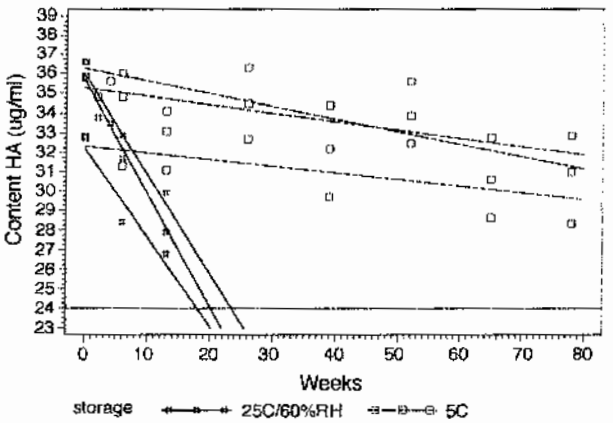

Fig. 5. Regression lines of haemagglutinin content on weeks per storage condition for each season and batch for B/Shangdong.

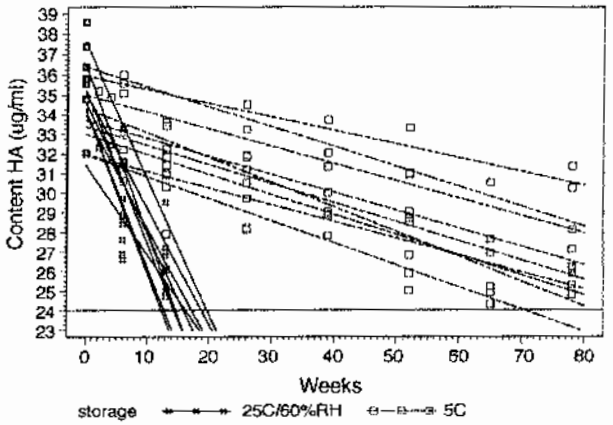

Fig. 3. Regression lines of haemagglutinin content on weeks per storage condition for each season and batch for A/Panama.

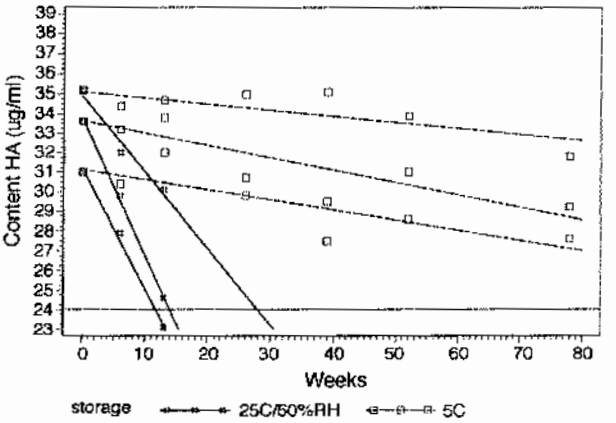

Fig. 6. Regression lines of haemagglutinin content on weeks per storage condition for each season and batch for B/Yamanashi.

Table 4
Regression coefficient for weeks as degradation rate dependent on storage with standard error, degrees of freedom, t- and p-value of t-test, from the analysis-of-variance with week depending on storage as co-variables and batch per season as explanatory factor, for each strain

Part 1	Estimated slope	Standard error	d.f.	t-value	p-value
A/New Caledonia					
25 °C/60% RH	−0.218	0.038	80	−5.8	0.000***
5 °C	−0.030	0.006	80	−5.2	0.000***
A/Panama					
25 °C/60% RH	−0.595	0.042	80	−14.0	0.000***
5 °C	−0.094	0.006	80	−14.5	0.000***
B/Guangdong					
25 °C/60% RH	−0.646	0.068	25	−9.5	0.000***
5 °C	−0.052	0.010	25	−5.2	0.000***
B/Shangdong					
25 °C/60% RH	−0.502	0.066	29	−7.6	0.000***
5 °C	−0.045	0.010	29	−4.7	0.000***
B/Yamanashi					
25 °C/60% RH	−0.567	0.054	22	−10.5	0.000***
5 °C	−0.049	0.009	22	−5.5	0.000***

Table 5
Regression coefficient for weeks as degradation rate dependent on storage with standard error, degrees of freedom, t- and p-value of t-test and 90% confidence interval, from the analysis-of-variance with weeks dependent on storage as explanatory variable and batch as explanatory factor, for each strain per thiomersal use

	Estimated slope	Standard error	d.f.	t-value	p-value	Lower	Upper
Part 2, thiomersal-containing							
A/New Caledonia							
25 °C/60% RH	−0.295	0.075	22	−3.9	0.001***	−0.423	−0.166
5 °C	−0.028	0.012	22	−2.3	0.032*	−0.049	−0.007
A/Panama							
25 °C/60% RH	−0.386	0.101	22	−3.8	0.001***	−0.559	−0.213
5 °C	−0.070	0.017	22	−4.2	0.000***	−0.098	−0.041
B/Yamanashi							
25 °C/60% RH	−0.444	0.090	22	−4.9	0.000***	−0.599	−0.288
5 °C	−0.010	0.015	22	−0.7	0.514	−0.035	0.016
Part 2, thiomersal-free							
A/New Caledonia							
25 °C/60% RH	−0.419	0.053	22	−7.8	0.000***	−0.511	−0.327
5 °C	−0.036	0.009	22	−4.1	0.001***	−0.051	−0.021
A/Panama							
25 °C/60% RH	−0.545	0.087	22	−6.3	0.000***	−0.694	−0.396
5 °C	−0.084	0.014	22	−5.9	0.000***	−0.109	−0.060
B/Yamanashi							
25 °C/60% RH	−0.449	0.055	22	−8.2	0.000***	−0.543	−0.355
5 °C	−0.018	0.009	22	−2.0	0.058	−0.033	0.003

Table 6
Estimated ratio of degradation rates of 25 °C/60% RH relative to 5 °C with 90% Fieller confidence interval, derived from the analyses-of-variance in Table 8

	Ratio of degradation rates	Ratio lower bound	Ratio upper bound
Part 1			
A/New Caledonia	7.3	5.3	10.3
A/Panama	6.4	5.6	7.2
B/Guangdong	12.3	9.5	17.4
B/Shangdong	11.3	8.3	16.8
B/Yamanashi	11.6	9.0	16.2
A/Panama at week = 0	10.4	7.9	13.0
B/Guangdong at week = 0	23.8	17.3	32.4

The strains A/Panama and B/Guangdong showed a decreasing degradation rate over time for storage condition 25 °C/60% RH. Therefore, also the ratio of the initial degradation rates are derived with a quadratic week effect for storage condition 25 °C/60% RH included in the analysis-of-variance.

Table 7
Estimated shelf life above 24 μg/ml with 90% Fieller confidence interval per storage condition, season and batch, based on the analysis-of-variance with weeks dependent on storage as explanatory variable and batch per season as explanatory factor, for A/Panama

Part	Storage	Season	Batch	Shelf-life lower bound	Estimated shelf-life	Shelf-life upper bound
1	25 °C/60% RH	2000/2001	1	12	14	16
			2	14	16	18
			3	18	20	23
1	25 °C/60% RH	2001/2002	1	12	14	16
			2	11	12	14
			3	14	15	17
1	25 °C/60% RH	2002/2003	1	17	19	21
			2	18	20	23
			3	14	16	19
1	5 °C	2000/2001	1	80	90	103
			2	88	99	112
			3	115	128	144
1	5 °C	2001/2002	1	79	88	100
			2	69	78	88
			3	87	97	110
1	5 °C	2002/2003	1	107	119	133
			2	117	130	145
			3	93	104	117

One-sided the confidence level for the lower bound is 95%.

degradation (slope of the lines) of the different batches at the different conditions and the standard errors can be calculated. The results of these calculations can be found in Table 4.

The data show that the A/Panama strain is the most critical strain with regard to stability. At 5 °C the degradation rate is two to three times that of the other strains. Whereas at 25 °C the degradation rate was similar for all strains tested except for the A/New Caledonia which showed a much slower degradation at 25 °C. The fact that A/Panama is the most sensitive strain is further underlined by the fact that this was the only strain that had a batch that went out of specifications (lower than 24.0 μg/ml) during the 78 weeks tested.

The results in the Figs. 2–6 and in Tables 4 and 5 show that the rate of degradation at 25 °C is much faster than the rate of degradation at 5 °C. The ratios between the storage conditions 25 °C/65% RH and 5 °C have been calculated (Table 6) together with the 90% confidence interval using Fiellers method. The upper bound had a one-sided confidence level of 95%.

Table 6 shows that degradation at 25 °C occurs 6–12 times faster than degradation at 5 °C. As stated before the A/Panama strain turned out to be the most sensitive strain. Therefore, this strain determines the final stability of the product. Since this strain represents a worst case scenario, the increase in degradation rate seen for this batch can be used to asses the effects of short term exposure of the vaccine to higher temperatures regarding stability.

It was found that for the worst batch during the worst season of the A/Panama strain the lower bound of the 90% Fieller confidence interval was 69 weeks at 5 °C. Since the shelf life is only 52 weeks it is clear that a minor additional degradation caused by a short term exposure to room temperature would not lead to a vaccine with a haemagglutinin content below the shelf life requirement of 24 μg/ml after 1 year. The

Table 8
Maximum number of weeks at storage condition 25 °C/60% RH with the remaining weeks in 1 year at 5 °C for a shelf life of precisely 1 year with 90% Fieller confidence interval for A/Panama per season and batch, based on the analysis-of-variance with week depending on storage condition and week squared for storage condition 25 °C/60% RH as co-variables and batch per season as explanatory factor

Part	Season	Batch	Maximum 25 °C/60% RH lower bound	Estimated maximum weeks at 25 °C/60% RH	Maximum 25 °C/60% RH upper bound
1	2000/2001	1	2.7	3.9	5.8
		2	3.5	4.8	7.0
		3	5.9	7.8	11.0
1	2001/2002	1	2.6	3.7	5.5
		2	1.7	2.6	4.1
		3	3.4	4.6	6.7
1	2002/2003	1	5.3	6.9	9.7
		2	6.0	7.9	11.2
		3	3.9	5.3	7.6

The lower bound on the weeks corresponds to a guaranteed shelf life of precisely 1 year at a one-sided 95% confidence level.

maximum number of weeks at 25 °C without impairing the 1 year stability claim at 5 °C was calculated based on a one-sided 95% confidence level for the lower bound for the worst batch. It was found that for this batch a 1.7 week exposure of the vaccine to room temperature would not shorten the given shelf life of one year. The use of such a vaccine within the labeled shelf-life period will not place the patient at additional risk. The results of these calculations can be found in Tables 7 and 8.

3.2. The results of the comparative study between the thiomersal-containing and -free influenza vaccine

The content of thiomersal found in all measurements on the thiomersal-containing samples was between 90 and 110 μg/ml. Therefore, there is no sign of thiomersal degradation during storage indicating that differences between thiomersal-free and -containing formulations are indeed an effect of the thiomersal. The stability of the vaccine is not affected by the presence of thiomersal. This is also illustrated in Table 5 in which the degradation rates at the different conditions are presented for the different batches. The statistical evaluation shows that the 90% confidence intervals of the thiomersal-containing and -free batches are merely overlapping at both 5 and 25 °C. As already mentioned in Section 3.1, the measured degradation rate is the same for thiomersal-free and -containing formulations.

4. Conclusions

The data presented in this study shows that the degradation rate of different influenza vaccine strains varies significantly. Variations with a factor of more than three were observed. An exposure of the subunit vaccine to temperatures above the proposed label storage conditions increases the degradation rate. However, statistical evaluation of the data obtained for the most sensitive strain (A/Panama) showed that even exposure during a 2 week period of the vaccine to room temperature would not adversely affect the shelf life claim of the influenza subunit vaccine. Moreover, this study showed that the presence of thiomersal in the solution has no effect on the stability of the vaccine.

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