



SOLVAY PHARMACEUTICALS

06 June 2006

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. 2006D-0083, CBER 200611

Dear Sir/Madam:

Reference is made to the above mentioned Federal Register Notice dated 10 March 2006 entitled, "Draft Guidance for Industry on Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines".

Solvay Pharmaceuticals respectfully submits comments to the draft guidance mentioned above.

Should you have any questions or require additional information regarding this request please contact me at 770-578-5620 or fax me at 770-578-5864.

Sincerely,

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**FDA/CBER
DRAFT GUIDANCE FOR INDUSTRY**

Docket No. 2006D-0083, CBER 200611

**“Draft Guidance for Industry on Clinical Data Needed to Support the Licensure of
Trivalent Inactivated Influenza Vaccines”**

Solvay Pharmaceuticals

1. Docket No. 2006D-0083, CBER 200611 entitled “Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines”

1.1 Split virus vaccines

The draft guidance makes no distinction between split and sub-unit influenza vaccines. There are clear differences between the two types of vaccines as has been demonstrated for six influenza vaccines currently licensed in Europe.¹ Influvac, Agrippal and Fluvirin are subunit vaccines which do not contain matrix proteins and have lower total protein content than the split virus vaccines, Vaxigrip, Begrivac and Influsplit/Fluarix. Differences in influenza antigen variety may affect efficacy, whereas differences in concentrations of nonviral compounds such as ovalbumin and endotoxin may lead to different reactogenicity profiles. Thus, the distinction is important and should be made, perhaps “split virus vaccines, including trivalent purified surface antigen vaccines.”

1.2 III.A.2: Non-inferiority clinical efficacy trials

The Agency should provide guidance for a non-inferiority margin. Furthermore, the required sample size of non-inferiority clinical efficacy trials is very large, due to the low secondary attack rate and high level of protection in the vaccinated group resulting in a low number of expected cases of influenza illness.

1.3 III.A.3: Size of safety database

It is recommended that “several thousand subjects receive the investigational vaccine.” It would be helpful if this “several thousand” would be specified.

1.4 III.A.3: Size of safety database on pediatric population

It is not clear from the guidance document how large the size of the safety database on the pediatric population should be. More detailed guidance on this topic would be helpful.

1.5 III.B.1.a (2nd bullet): Non-inferiority margin for seroconversion rate difference

It is often not clear if a margin for a rate (proportion) is relative or absolute. Here the margin is absolute. To avoid confusion we suggest the wording "10 percent points" instead of "10%."

1.6 III.B.1.a/C.2: Non-inferiority margin for the geometric mean ratio

The non-inferiority margin for the geometric mean ratio (1.5) is very strict. To be secured of sufficient statistical power the required total sample size for non-inferiority immunogenicity trials is 920, and that for lot consistency studies 1000. We propose a less strict margin: 2.0. To compensate for this less strict margin proof of assay sensitivity could be required by the agency (see below).

The statistical analysis of a non-inferiority immunogenicity trial involves calculating, per vaccine strain, the upper bound of the two-sided 95%-confidence interval for the geometric mean ratio (GMR) of the post-vaccination geometric mean titers (GMTs): $\text{GMT}_{\text{US licensed vaccine}} / \text{GMT}_{\text{new vaccine}}$. According to the draft document non-inferiority can be concluded if for all three strains the bound does not exceed 1.5.

The non-inferiority margin 1.5 for the GMR corresponds to the non-inferiority margin $\delta = \log_2[1.5] = 0.585$ for the mean difference of log-transformed HI titers. (Transformation: $\log_2[\text{HI titer}/5]$, see the attached manuscript on the statistical analysis of lot consistency studies for a rationale; review paper, to appear in the *Journal of Biopharmaceutical Statistics*, special issue on vaccines (2006).)²

Let $(1-\beta)$ denote the statistical power of the trial for a single strain (= probability that non-inferiority is demonstrated for that particular strain), then for the overall statistical power P (= probability that non-inferiority is demonstrated for all three strains) the following inequality holds:

$$P \geq (1-\beta)^3$$

Thus, to be secured of an overall statistical power of (at least) 0.90 the power for a single strain should be 0.965. An approximate sample size formula for the number of subjects per vaccination arm is:

$$n = 2(Z_{1-\beta} + Z_{1-\alpha/2})^2 \sigma^2 / (|\delta| - |\Delta|)^2$$

with $Z_{1-\beta}$ and $Z_{1-\alpha/2}$ the upper 100(1- β) and the 100(1- $\alpha/2$) upper centiles of the standard normal distribution, σ the standard deviation of log-transformed HI titers, δ the non-inferiority margin and Δ the true but unknown mean difference between the vaccines.² In order not to overestimate the power of the trial it is advisably not to assume that $\Delta = 0$, but that $\Delta > 0$, say, $\Delta = 0.15$. An estimate for the standard deviation of log-transformed HI titers is $\sigma = 1.75$. With $Z_{0.965} = 1.81$, $Z_{0.975} = 1.96$, it follows that with $\delta = 0.585$:

$$n = 2(1.81 + 1.96)^2 1.75^2 / (0.585 - 0.15)^2 = 460$$

Hence, the required total sample size of the study would be 920 subjects.

The proposed, less strict non-inferiority margin 2.0 for the GMR corresponds to $\delta = 1.0$. In that case the required number of subjects per arm would be:

$$n = 2(1.81 + 1.96)^2 1.75^2 / (1.0 - 0.15)^2 = 120$$

i.e. a required total sample size of 240 subjects.

For a justification of the margin 2.0 (corresponding to one titration step) we refer to the argumentation in the section *Choice of equivalence margin* of the attached manuscript.³

For lot consistency trials even larger sample sizes would be required. For a possible statistical analysis of lot consistency data, see the attached manuscript. The statistical power can be investigated by means of computer simulations. The non-inferiority margin 1.5 would imply a required total sample size of approximately 1000 subjects. In contrast, margin 2.0 would imply a required total sample size of approximately 450 subjects.

Assay sensitivity is not mentioned in the draft document. Assay sensitivity is defined as the ability to distinguish an effective treatment from a less effective or ineffective treatment. Lack of assay sensitivity may lead to an erroneous conclusion of efficacy. This

may happen if efficacy is demonstrated by showing that a new treatment is not inferior to a reference treatment, and the reference treatment was not effective. A possible criterion for assay sensitivity could be that for both vaccines the CHMP requirement for vaccine immunogenicity is met.⁴

1.7 III.B.1.b: Age groups

The draft guidance defines the adult age group as < 65 and the elderly age group as ≥ 65 years of age. The European CHMP guidelines define the adult age group as ≤ 60 and the elderly age group as > 60 years of age. In the interests of global standardization the Agency should consider working to harmonize the definition of these age groups.

1.8 III.B.1.b: Confidence interval for seroconversion and seroprotection rates

The appropriateness of confidence interval for single means (e.g., rates) in clinical trials is a matter for debate. The view of Solvay Pharmaceuticals on the appropriateness of confidence intervals for the CHMP parameters was presented on a poster during the Second European Influenza Conference (Malta 11–14 September 2005)⁵. Below we summarize our view. The full text of our poster is attached.

It is sometimes argued that the European CHMP criteria for influenza vaccine immunogenicity can be improved by introducing more stringent criteria. For example that the lower bounds of the two-sided 95% confidence intervals for the parameters must exceed the limits, instead of the values of the parameters themselves. The motivation for this proposal is that if, for instance, the seroprotection rate exceeds 70%, this does not prove that the true seroprotection level in the target population also exceeds the limit, but if the lower confidence bound falls above the limit we can be confident that the true level exceeds 70%.

Confidence intervals for single group means are interpretable only if the subjects constitute a random sample from a well-defined population.⁶ In influenza vaccine studies this is seldom, if ever, the case. So, what is the seroprotection rate a measurement of in an influenza vaccine study? Definitely not the fraction of the target population that would become seroprotected if vaccinated, because the subjects in the study are not a random

sample from the population. Likewise, the confidence interval for the seroprotection rate is not an interval estimate of a population fraction.

1.9 III.C.2: Safety laboratory tests

In contrast to the other guidance document safety laboratory tests are not mentioned. Is this to be understood that for the licensing of trivalent inactivated influenza vaccines these safety laboratory tests are not mandatory? That would be in line with common practice.

References:

1. Chaloupka A, *et al.* Comparative analysis of six European Influenza Vaccines. *European Journal of Clinical Microbiology and Infectious Diseases* 1996; **15**: 121-127.
2. Julious SA. Tutorial in biostatistics: sample sizes for clinical trials with normal data. *Statistics in Medicine* 2004; **23**: 1921-1986 (section 4.1).
3. Nauta J. Statistical Analysis of Influenza Vaccine Lot Consistency Studies, Review paper to appear in the Journal of Biopharmaceutical Statistics (2006)
4. CPMP/BWP. Note for guidance on harmonization of requirements for influenza vaccines (CPMP/BWP/214/96), 12 March 1997. [<http://www.emea.eu.int/pdfs/human/bwp/021496en.pdf>]
5. Nauta J. and deBruijn I. The European CHMP Criteria for Influenza Vaccine Immunogenicity cannot be Improved by the Use of Confidence Intervals. Second European Influenza Conference (Malta 11–14 September 2005).
6. Senn S. Added Values. Controversies concerning randomization and additivity in clinical trials. *Statistics in Medicine* 2004; **23**: 3729-3753.