

CMC Review, January 25, 2010 - Flublok

DRAFT

DATE: January 25, 2010

FROM: Matthew Sandbulte, PhD

THRU: Jerry Weir, PhD

CC: Maryna Eichelberger, PhD

Anissa Cheung, PhD

SUBJECT: BLA STN 125285: Sponsor Responses to CR Letter (August 29, 2008) and IR Letters (July 30, 2009; October 1, 2009; November 6, 2009), and Strain Change Supplement (September 18, 2009)

PRODUCT: Influenza recombinant HA trivalent

SPONSOR: Protein Sciences Corp.

This CMC review memo deals with CBER comments 3 and 4 (multiple-part comments) in the Complete Response letter sent to Protein Sciences on 29 August 2008. CBER also submitted follow-up queries in Information Request (IR) letters dated 30 July 2009, 1 October 2009, and 6 November 2009. Another item, besides those in comments 3 and 4, arose in the strain change update amendment dated 09/18/2009; it was not fully resolved when a second CR letter was issued on 11 January 2010. This memo evaluates Protein Sciences' responses provided over multiple submissions:

- Reply to the 29 August 2008 CR Letter (Amendment 13)
- Reply to the 30 July 2009 IR Letter (Amendment 19)
- Strain change supplement, 18 September 2009
- Reply to the 1 October 2009 IR letter (Amendment 22)
- Reply to the 6 November 2009 IR letter (amendment dated December 11, 2009)
- Reply to portions of several CBER communications (amendment dated December 18, 2009)

CMC review summaries, and accompanying comments / questions to the sponsor, were composed in response to each submission by PSC. This memo organizes these sequential summaries, comments, and questions under section headings of the CR Letter (bold font).

Summary of key issues:

Based on doses administered in clinical trials and data from product stability studies, CBER and Protein Sciences came to agreement on the following: FluBlok will be formulated to a target SRID potency of (b)(4) HA per dose for each strain. The minimum and maximum release specs are (b)(4) and (b)(4) per dose, respectively. The minimum potency spec through expiry is (b)(4) HA per dose.

CBER accepted PSC's proposed release spec for total protein in FluBlok product:-- (b)(4)--- per dose, measured by the BCA assay.

In monovalent bulk drug substance release testing, the lower limit for -----
----- (b)(4) ----- . At the
stage of FluBlok product blending, the ----- (b)(4) ----- of each monovalent bulk
component will be retested and must remain (b)(4).

PSC observed formation of visible particles in some monovalent bulk batches.
Preliminary experiments showed that removing particles by filtration had little effect on --
-- (b)(4) ----- . PSC has committed to more in-depth analysis of particles in
various batches from the past two years, but no report has been issued to CBER. This
unresolved issue was conveyed in the 11 January 2010 CR letter.

Based on SRID data from two years' worth of monovalent bulk stability studies, PSC
proposed shelf lives of ----- (b)(4) ----- for recombinant H1, H3, and B
HA, respectively. It was estimated that these expiry periods ensure each lot used to
formulate final product will retain at least (b)(4) of its initial potency.

DNA content of final product will be release tested by --- (b)(4) -- assay, with a release
spec of ≤ 10 ng per dose. ----- (b)(4) -----
----- .

HA gene reference sequences for each recommended vaccine strain shall be defined
based on sequence data posted to public databases (such as NCBI) or supplied directly
by CDC. If the amino acid sequence encoded by a cloned rHA vaccine component is
not absolutely identical to that encoded by the corresponding reference sequence,
antigenic similarity between the variant rHA and the reference strain must be
demonstrated serologically. This unresolved issue was conveyed in the 11 January
2010 CR letter.