which samples will be evaluated for phenotypic stability and does not envision a need for a modified assay. In addition, it is worth noting that the original *ts* phenotype assay was not formally validated for use with clinical study samples. If a situation should arise where there is a need to evaluate the phenotypic stability of shed vaccine viruses MedImmune proposes that this would again be evaluated through use of sequencing data as the 5 major determinants that control the *ts* phenotype have been extensively characterized (Jin et al, 2003).

CHMP comments: Issue solved.

Regarding the sequencing data, the MAH should clarify if deep sequencing has been envisaged.

MAH answer

Deep sequencing (massive parallel sequencing) of virus samples has been considered as a technical approach to understand genetic population distribution of shed vaccine virus. Nucleotide diversity is expected to be observed in influenza viruses, as negative strand RNA viruses have low fidelity polymerase and the mutational frequency is estimated at 1:10,000 nucleotides.

Because a priori definitions for acceptance criteria were deemed problematic, and consideration for qualifying and validating deep sequencing as an analytical method for clinical samples was determined not to be feasible, this approach was not considered further.

CHMP comments: Issue solved.