Administrative Notice
November 25, 2025

To: Pharmaceutical Affairs Section, Prefectural Health Department (Bureau)

Medical Device Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare

Questions and Answers (Q&A) on "Evaluation for shedding associated with gene therapy products using viruses/vectors"

Evaluation of shedding associated with gene therapy products using viruses/vectors is discussed in the "Evaluation for shedding associated with gene therapy products using viruses/vectors" (Administrative Notice dated November 25, 2025 by Medical Device Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare).

As provided in the attachment, questions and answers related to this administrative notice are compiled. Please inform the relevant business operators in your jurisdiction thoroughly of this matter.

Attachment

Q&A on "Evaluation for shedding associated with gene therapy products using viruses/vectors"

Question 1 Concerning "In addition, they may be included in the post-marketing risk management plan, depending on the situation." at Lines 7 and 8 on Page 5, in which situations do you consider it desirable to include them in the post-marketing risk management plan?

(Answer) At present, no specific examples are available, but a post-marketing risk management plan is highly likely to include them when clinical studies have had situations where special risk management is needed in addition to general risk management such as information provision using materials such as a package insert.

Question 2 Concerning "For example, viruses/vectors derived from viruses that can stay latent after infection and may be reactivated, such as herpes simplex virus (HSV) known to cause latent infection, may start shedding upon reactivation. For this reason, to evaluate extended shedding or post-reactivation shedding, an appropriate long-term study plan may be needed." at Lines 23 to 27 on Page 6, is there any potentially appropriate period in terms of how long shedding studies should be continued if the vector is derived from viruses that may cause latent infection?

(Answer) General incubation periods of wild-type viruses can be used as reference. In addition to the above, considerations should be given to characteristics of the genetically modified organism, tissues supposed to be involved in incubation based on the route of administration, and possibility of reactivation, when necessity of a long-term study and period of the concerned study are discussed.

Question 3 Concerning "a combination of molecular biological and biological techniques can overcome limitations of each assay in general." at Lines 20 and 21 on Page 8, what kind of assays are assumed for the "combination"?

(Answer) If a high-sensitivity NAT provides a positive signal, a biological technique using cells may be separately applied to determine whether the positive signal is derived from infectious viruses.

Question 4 Concerning "1) NAT-based analytical procedures" at Lines 9 to 31 on Page 9, may qPCR/ddPCR-based analytical procedures mentioned in the "Nonclinical Biodistribution Considerations for Gene Therapy Products" (PSB/MDED No. 1023-1, dated October 23, 2023) (hereinafter referred to as "ICH S12") be deemed applicable?

(Answer) Yes.

Question 5 Concerning "For this reason, to evaluate shedding of viruses/vectors with the intact genome, use of multiplex NAT and droplet digital PCR (ddPCR) capable of amplifying sequences at multiple target sites simultaneously should be considered where possible. Efforts should be exerted to obtain more accurate information." at Lines 16 to 19 on Page 9, why the multiplex NAT and ddPCR capable of amplifying sequences at multiple target sites simultaneously were

assessed as “More accurate”?

(Answer) The multiplex NAT and ddPCR capable of detecting multiple sequences simultaneously can acquire the ability to determine whether the detected genome sequences are derived from small fragments or nucleic acids of a certain length by designing both terminal sequences of the virus genome as ones to be detected. Compared with PCR, which targets a single site, and thus provides no information on the genome length, these techniques are expected to be more accurate.

Question 6 Concerning “Sensitivity of NAT for each tissue specimen should be determined using the specimens spiked with the NAT reference standard containing a known amount of virus/vector sequences and documented.” at Lines 25 to 27 on Page 9, may naked-plasmid or the like be used in place of viruses/vectors as the “NAT reference standard”?

(Answer) If naked-plasmid or the like is used, the nucleic acid extraction efficiency cannot be evaluated or may be underestimated, in particular, for RNA viral vectors. The appropriate NAT reference standard available for evaluation of the nucleic acid extraction efficiency should be selected.

Question 7 Concerning “Infectivity assays are required to have adequate sensitivity and reproducibility and should be performed with a sufficient number of specimens.” at Lines 8 and 9 on Page 10, to what extent of detection sensitivity do you assume “adequate sensitivity”?

(Answer) This will be on a case-by-case basis according to characteristics of viruses/vectors.

Question 8 Concerning “The desirable evidence is results from biodistribution and shedding studies with multiple analogous viruses/vectors.” at Lines 26 and 27 on Page 11, if shedding studies in clinical studies are planned only based on past information of analogues viruses/vectors without conducting nonclinical shedding studies, what kind of study results should be used to explain similarity of the characteristics?

(Answer) For scientific justification, results to be used for explanation should demonstrate that multiple analogous vectors exhibit similar shedding patterns irrespective of the type of genes integrated.

Question 9 Concerning “In nonclinical shedding studies, animal species in which reactions to viruses/vectors are similar to those in humans should be desirably selected as done in other nonclinical studies such as Proof-of-Concept (PoC) and safety studies.” at Lines 2 to 4 on Page 12, if there are no appropriate animal species that exhibit reactions similar to those in humans, what actions should be taken?

(Answer) Even if there are no appropriate animal species, conducting nonclinical shedding studies should desirably be considered as long as such studies are expected to provide certain information. In addition, for planning shedding studies in clinical studies, utilization of data on shedding of wild-type viruses in humans should be considered. Of note, if evaluation in nonclinical shedding studies has limitations, clinical shedding studies should be planned to obtain information on shedding in humans as much as possible.

Question 10 Concerning “Shedding studies in animal models of the disease are supposed to have difficulty complying with the Good Laboratory Practice (GLP) when conducted. Such studies, which may inevitably finish in a non-GLP status, should be conducted in compliance with the GLP wherever possible to ensure the data integrity to the extent possible.” at Lines 22 to 25 on Page 12 and “Sample analysis for BD can be conducted in a non-GLP manner.” In the ICH S12, can similar principles be applied to analytical procedures for shedding?

(Answer) Yes.

Question 11 Concerning “For example, sampling in clinical studies may be of little significance for viruses/vectors that are theoretically unlikely to shed and actually did not shed in nonclinical studies.” at Lines 9 to 14 on Page 14, please provide specific examples.

(Answer) For example, if replication incompetent viruses/vectors to be administered at isolated sites in the body such as the brain have not exhibited shedding into body fluids in nonclinical studies, omission of sampling over time in clinical studies may be decided.

Question 12 Concerning “On the other hand, for viruses/vectors such as ones derived from AAV that may persist for a long period of time but are not expected to replicate in the body, sampling and assays may be terminated when assay results show a consistent decreasing trend or a stable plateau phase, even though the amount of shed viruses/vectors has not reached the lower limit of detection of the assay.” at Lines 5 to 8 on Page 17, how long and to what extent do you assume for the consistent decreasing trend?

(Answer) Although it depends on sampling schedule, the longer is better. It should be decided on a case-by-case basis according to characteristics of viruses/vectors.

Question 13 Concerning “Because patients are kept under certain control with the limited number of patient contacts in clinical studies, extensive transmission to third parties is considered unlikely to be identified during clinical studies even if the viruses/vectors have a transmission risk owing to the properties. Consideration should be given to inclusion of evaluation about the transmission in product pharmacovigilance activities and post-marketing surveillance.” at Lines 23 to 26 on Page 21, is there any specific method of information collection for the surveillance?

(Answer) In the product pharmacovigilance activities and post-marketing surveillance, measures to ensure close two-way exchange of information between the marketing authorization holder and healthcare professionals must be considered. For example, the marketing authorization holder may provide healthcare professionals with information about characteristics of viruses/vectors that may be related to transmission to third parties and establish a contact point that accepts such information from healthcare professionals.

End of Document