

**Oncolytic viruses:
Considerations for the evaluation of Shedding¹**

VERSION 2

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Version 1	December 2020	
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¹ This document has not been adopted by the European Commission and, therefore, it does not contain the official position of the European Commission.

I. Introduction

Oncolytic viruses may be used in a clinical setting to treat malignancies. Oncolytic viruses may consist of attenuated strains of viruses with an inherent capacity to selectively infect and/or replicate in and destroy tumour cells, or engineered viruses designed to selectively infect and/or replicate in and destroy tumour cells. Examples of oncolytic viruses include, among others, adenovirus, herpes simplex virus, vaccinia virus, measles virus and reovirus.

From an environmental standpoint, one of the main concerns linked to the administration of medicinal products based on oncolytic viruses is the release of oncolytic virus through secretions and/or excreta of the patient (“shedding”).

This document has been endorsed by the national competent authorities of the following Member States: Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, the Netherlands, Portugal, Romania, Slovenia, Spain, Sweden and Norway.

II. General principles

1. It is expected that shedding is addressed as soon as possible in the clinical development.

Available information from the same oncolytic virus strain or serotype may be used to inform conclusions on shedding and/or to inform the design and extent of the shedding studies.

If changes are introduced, extrapolation may be possible if those changes do not alter the pathogenic or virulent profile, tropism, ability to replicate and/or shedding profile of the virus. Additionally, consideration should be given to the location of the targeted tumour(s) and metastasis and the route of administration and the administered dose in order to assess to what extent extrapolation of data from a previous medicinal product may be possible. The applicant should provide a justification on the relevance of the already available information.

2. At the beginning of the clinical development, if there is no previous clinical experience with the same oncolytic virus strain or serotype, the potential for shedding can be assessed based on available relevant non-clinical shedding and/or biodistribution data.

In general, if relevant data is not available, shedding should be assumed and appropriate risk-minimisation measures should be put in place.

3. During the conduct of a clinical trial with oncolytic viruses it is generally expected that information is collected on the shedding potential of the medicinal product. However, the

absence of collection of shedding data may be justified when information is available from previous trials or previous clinical experience with the same oncolytic virus strain or serotype. For example, if sufficient data on shedding has been obtained during the early clinical development, the omission of shedding analysis in the confirmatory trial may be justified.

4. A risk-based approach should be applied to determine the design and extent of shedding studies, as well as -where applicable- in the definition of appropriate risk minimisation measures (“RMMs”). Among others, the following aspects should be taken into consideration:
 - i. *Pathogenicity of the wild type virus.* The level of effort in characterising the shedding profile of the medicinal product should be adjusted to the pathogenicity of the wild-type virus. In the case of pathogenic viruses, a comprehensive study of the shedding profile in non-clinical studies is expected before the medicinal product is administered to humans. Likewise, comprehensive collection of shedding data during the clinical trial is also expected. In contrast, less detailed data may be acceptable if the medicinal product is derived from low pathogenic viruses, provided that no modification has been introduced that may render the recombinant virus more pathogenic or virulent.
 - ii. *Available information on tropism of the oncolytic virus:* Where relevant, it should be considered whether the virus/vector itself has been genetically modified to alter the cellular/tissue tropism compared to the wild-type strain or serotype.
 - iii. *Host range:* The level of effort in characterising the shedding profile of the medicinal product should take into account whether the virus affects humans only or if it is capable of infecting other species. Where animals are susceptible of being infected, efforts should be stepped up also in the implementation of risk minimisation measures.
 - iv. *Availability of treatment:* If there is no treatment available against the infection with the wild type virus, efforts in the characterisation of the shedding profile and in the implementation of the risk minimisation measures should be stepped up.
 - v. *Attenuating modifications introduced in the recombinant virus:* Oncolytic viruses can be modified to attenuate their ability to replicate in non-tumour cells, or to reduce virulence or latency in the treated patients. While these modifications can alter the shedding profile of the medicinal product (vis-à-vis the wild-type virus), the stability of the attenuating modifications should be duly taken into account. In particular, the potential for recombination or genotype reversion should be considered and, as appropriate, specific RMMs should be implemented.

III. Non-clinical studies

Shedding data from animal studies can help understand the shedding profile of oncolytic viruses in humans. Virus shedding analysis can be integrated as part of other non-clinical studies. However, animal models present inherent limitations, such as different permissiveness of the virus in animals compared to humans or pre-existing immunity that may affect infectivity or virus clearance. For that reason, absence of viral shedding in an animal study may not be enough justification to waive the collection of shedding information during the conduct of the clinical trial.²

Where there is relevant prior experience in humans (same oncolytic virus strain or serotype and the same route of administration), the generation of new shedding data in non-clinical studies may not be required. In such cases, risk minimisation measures according to the shedding profile and identified risks should be implemented during the conduct of the clinical trial.

IV. Collection of shedding data in clinical studies

1. Samples:

The types of samples that should be collected depends on the specific characteristics of the medicinal product, taking due account of the following elements:

- i. *Route of transmission and shedding pattern of the wild-type virus.* For example, if the wild-type virus spreads through aerosols, samples to be considered include saliva and nasopharyngeal swabs.
- ii. *Tropism of the oncolytic virus.*
- iii. *Route of administration of the medicinal product:* For example, if a medicinal product is administered intra-dermally the shedding study should consider the risk of shedding from the administration site. To this end, the collection of skin swabs from the injection site is expected.
- iv. *The location of the tumour.* For example, if the tumour is located in the oral cavity, larynx, pharynx or oesophagus, collection of saliva samples is expected.

2. Duration of monitoring:

The duration of monitoring of shedding should be decided case-by-case taking due account of the following elements:

- i. *Characteristics of the wild-type strain from which the investigational medicinal product is derived.* For example, if the wild-type virus is known to be persistent, consideration should be given to a longer duration of the shedding monitoring.

² However, it may be possible for the sponsor to implement strict risk minimisation measures for the early phases and to collect shedding information in later phases.

- ii. *Replication competence.* The potential for shedding is typically higher in case of replication-competent oncolytic viruses as such virus may be present in the treated patient for a prolonged period of time and can increase in amount, thereby affecting the extend and duration of shedding.
- iii. *Immune status of the patient population:* in case of immune-incompetent patients, the clearance of the virus may be slower than in case of immune-competent patients. Therefore, if the medicinal product is intended to be administered to immunosuppressed patients, the duration of the shedding studies may need to be longer.

Sample collection and analysis should continue until multiple consecutive negative samples are detected. The time points chosen should be relevant considering also the need to detect viruses derived from the viral replication in the tumour cells. A justification for an alternative approach may be provided.

However, if the medicinal products are based on a virus that has the potential for latency reactivation, absence of viral shedding at specified time period cannot exclude shedding at later time point. In such cases, the possibility for delayed shedding should be considered as part of the environmental risk assessment and –where appropriate, having regard to the specific characteristics of the product - control measures should be considered.

V. Analytical Assays

Detection methods used should be suitable to detect the shedding of the recombinant virus.

The test methods used to assess shedding potential of the oncolytic virus should be sufficiently sensitive. The submitted data should be accompanied by an explanation of the quality parameters (*e.g.* limit of detection, specificity). Qualified analytic methods should be used.

It is recommended to follow a step-wise approach. As a first step, quantitative PCR based assay to detect viral/vector genetic material (qPCR) is recommended. qPCR does not permit to differentiate between intact virus with potential for infection and degraded viruses that can no longer infect. Therefore, as a second step, it is recommended to assess infectivity. Data on infectivity should be considered when proposing RMMs.

If the amount of shed material detected by qPCR is below the detection limit of the infectivity assay, it may be justified not to do the infectivity assay.

Where analytical methods are used which do not allow distinguishing between infectious and degraded virus, the assumption should be made that the shed material is infectious.

VI. RMMs

Risk minimisation measures should be implemented to minimise exposure of thirds, including healthcare professionals and close contacts. Particular attention should be paid to minimising the exposure of immunocompromised individuals and other vulnerable populations.

The need for specific risk minimisation measures should be assessed having regard to the identified risks, taking into account *e.g.* the identified shedding potential, the potential of the oncolytic virus to replicate in the environment, as well as aspects such as the ability of the shed virus to survive on surfaces and in water. For example, it might be appropriate to provide instructions to the patient and family members to minimize the exposure of others, including recommendation of specific sanitation measures.

Finally, it is expected that, if animals may be infected, appropriate measures to limit exposure to susceptible pets or other animals in the immediate surroundings of the treated patient should be considered.

The following table illustrates possible risks minimisation measures that could be considered when shedding cannot be excluded and when the recombinant virus poses a risk for human health and the environment. It is emphasized that these measures are provided for illustration purposes only and a case-by-case analysis is required.³

Shedding via direct contact or respiratory route	<p>Appropriate infection control measures should be implemented to minimize the environmental risk; <i>e.g.</i>:</p> <ul style="list-style-type: none"> ▪ Recommendations of good hygiene practices to patients/carers: <ul style="list-style-type: none"> ○ cover mouth and nose while coughing or sneezing with a single-use tissue and dispose dirty tissues after use; ○ frequent washing of hands with soap and water or use of alcohol-based products. ▪ Clothes, household linens, including cleaning cloths, should be washed at least at 60 °C on a regular basis. The home should be cleaned regularly with standard household cleaners. ▪ Measures of social distancing should be considered, in particular with regard to immunocompromised persons or vulnerable populations (avoid touching, kissing or hugging, avoid sharing of eating utensils or drinking glasses). ▪ Patients with respiratory symptoms (<i>e.g.</i> running nose, coughing) should avoid crowded or poorly ventilated public places and, where applicable, avoid contact to susceptible animals or pets.
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³ Additional measures may be required in cases where the contained use framework is applied with a view to prevent that there is release into the environment.

Shedding from bodily fluids	Measures to avoid exposure of vulnerable population should be generally considered.
<i>Shedding from urine/stools</i>	<p>Instructions on hygiene procedures should be provided to patients/carers (<i>e.g.</i> hand washing, cleaning of surfaces that were in contact with bodily fluids, use of separate toilet (if possible), adding bleach or equivalent products to toilet after each use, no sharing of utensils such as towels).</p> <p>In case of paediatric patients, disposable diapers should be sealed in two plastic bags before they are disposed in household waste. Other measures may be necessary such as adding bleach into the sealed plastic bags.</p>
<i>Shedding from saliva</i>	Recommendations to minimize exposure of thirds should be provided to patient/caretakers (<i>e.g.</i> no kissing, no sharing of eating utensils or drinking glasses, <i>etc.</i>)
<i>Shedding from sperm or vaginal secretion</i>	Sexual abstinence or use of condoms should be recommended to patients and/or sexual partners.
Shedding from injection site, pustules or wounds	<p>Instructions on the use of occlusive or non-occlusive dressing should be provided to patients/carers, including the recommendation to use protective clothing (gloves) when changing/handling dressings. In addition, instructions for the disposal thereof should also be provided (used dressings should be put in sealed bag and thrown to household waste or brought back to the study site for disposal).</p> <p>Kits containing all materials needed for changing the dressing can be provided (gloves, new dressing, waste bag, <i>etc.</i>).</p> <p>Vulnerable populations should avoid direct physical contact of the administration site, pustule/wounds and contaminated materials. In certain cases (<i>e.g.</i> for vaccinia oncolytic virus), patients may be instructed to return the bags with the used occlusive dressings to the clinical trial site for disposal.</p>