Svar fra VKM på oppdrag om vurdering av søknadskjema og veiledningsdokumenter utarbeidet i GMO-interplay: del III

Vurdering av EUs generelle søknadskjema for virusvektorer: "Common application form for viral vectors contained in investigational medicinal products for human use"

Søknadsskjemaet omfatter virus-vektorer generelt med unntak av Adeno-assosierte virus-vektorer (AAV-vektorer). Det er et eget skjema for AAV-vektorer. Det skjemaet har VKM har vurdert tidligere.

Ordliste

Klinisk vektor (clinical vector): Ekvivalent til virus-vektor.

Foreldrevirus: Den varianten av et virus som var utgangspunkt for konstruksjon av en virus-vektor. Foreldrevirus er en bestemt stamme av et virus, og ofte en svekket variant.

Rekombinasjon: Metoder for å sette sammen (rekombinere) biter av DNA

Replikasjonskompetent: virus eller virusvektor som kan replikere i celler og danne dattervirus som igjen kan infisere nye celler.

Revertere: Mutere tilbake til den opprinnelige variant.

Transgen: Gen(er) som uttrykkes av virus-vektor

Villtypevirus: Et normalt forekommende virus variant som ikke er svekket verken ved genregulering eller cellekulturdyrking

Virus overlevelse: Vanligvis anser man ikke virus om levende, og derfor er ikke «overlevelse» et korrekt uttrykk, men det er beskrivende. I denne sammenheng (og i de fleste andre sammenhenger) menes hvor lenge et virus er infeksiøst, det vil si har beholdt evnen til å kunne infisere.

(Bioteknologirådet har en stor og god ordliste/ordforklaringer)

Kort om virus vektorer

Når et virus brukes som vektor (virus-vektor) er de delene av virusgenomet som er nødvendige for ekspresjon av de innsatte gener, «rekombinante gener», beholdt. Dersom en virus-vektor skal kunne replikere og danne dattervirus som igjen kan infisere nye celler, det vil si være replikasjonskompetent, må store deler av genomet til det opprinnelige viruset «foreldreviruset» være intakt. Dette kan for eksempel være aktuelt ved bruk av et virus som vektorvaksine for en sykdom forårsaket av et annet virus. Et eksempel på en replikasjonskompetent viral vektorvaksine er rVSV-ZEBOV-vaksine mot ebola.

Dersom man ikke ønsker at en virus-vektor skal være replikasjonskompetent fjernes større deler av foreldrevirusgenomet. Virus-vektor med rekombinante gener pakkes da som viruspartikler i celler som uttrykker de gener som ble fjernet fra foreldreviruset da man konstruerte virus-vektoren. De pakkede virus-vektorene vil inneholde de aktuelle rekombinante genene og uttrykke disse når partiklene infiserer/transduserer humane celler i «pasienten/mottager».

Det er begrensede mengder med rekombinante gener de ulike virus-vektorer kan pakke, egentlig begrenset av hva det er plass til i virus partikkelen. Men viruspartikler som kan «vokse» i lengde, som for eksempel VSV i rhabdovirus-familien, kan pakke relativt store mengder nukleinsyrer.

Virusreplikasjon foregår i cellekjernen for noen virusfamilier og i cytoplasma for andre. Enkelte virusgenomer integreres i arvematerialet til cellen som en normal del av replikasjonssyklus og for andre virus er det ikke kjent å kunne skje. Dersom det er ønskelig med ekspresjon over et lengre tidsperspektiv i de cellene som infiseres/transduseres av virus-vektoren kan det være gunstig å bruke virus-vektor hvor integrasjon av foreldrevirusgenomet i cellegenomet er en naturlig del av syklus. Dersom dette ikke er ønskelig, er det være gunstig å bruke virus-vektor hvor integrasjon i av foreldrevirusgenomet ikke er kjent.

Aktuelle typer virus vektorer

Per november 2021 kjenner VKM til følgende virus-vektor-typer til bruk/utprøving i humanmedisin:

Humane legemidler godkjent i Norge

Adenovirus

- Luxturna®, Novartis; Øyemiddel. Innholdstoff Voretigen neparvovek er en genoverføringsvektor som bruker et adenoassosiert virusvektor serotype 2 (AAV2)-kapsid som leveringsvehikkel for humant retinalt pigmentepitel 65 k
- Zolgensma®, Novartis Gene Therapies; mot spinal muskelatrofi. Inneholder Onasemnogenaberparvovek. Virus vektor er ikke-replikerende rekombinant adenoassosiert virus serotype 9 (AAV9)-basert vektor som inneholder cDNA fra det humane SMN-genet under kontroll av cytomegalovirus promotor/hønse-β-aktin-hybrid-aktivator.

Lentivirus

- Kymriah®, Novartis; CAR-T-behandling. Innholdsstoff tisagenlekleucel er autologe T-celler som er genetisk modifisert ex vivo ved hjelp av en lentiviral vektor som koder for en kimær anti-CD19 antigenreseptor (CAR).

Herpesvirus

- Imlygic®, Amgen; Antineoplastisk og immunmodulerende middel. Inneholder Talimogenlaherparepvek som er en onkolytisk immunterapi som er utledet fra HSV-1. Talimogenlaherparepvek er et svekket herpes simplex type 1-virus (HSV-1) som er avledet ved funksjonell sletting av 2 gener (ICP34.5 og ICP47) og innsetting av kodingssekvens for human granulocyttmakrofagkolonistimulerende faktor (GM-CSF); CAR-T-behandling.

Spørsmål fra MDir:

2.1 *Etter VKMs vurdering, er søknadskjemaet i tråd med kravene til vurdering av helse og miljørisiko, og vil VKM kunne foreta en helse- og miljørisikovurdering av GMOen brukt i det kliniske studiet på bakgrunn av opplysninger som fremkommer i skjema?*

VKM kan gjerne besvare dette spørsmålet todelt, i form av en tabell som viser at alle deler av søknadsskjemaet er vurdert, og med en påfølgende konklusjon som skriftliggjør på hvilket grunnlag har VKM gjort denne vurderingen, og at de momenter i vurderingen som er tillagt mest vekt av VKM kommer tydelig frem.

VKM har vurdert om søknadsskjemaet «Common application form for viral vectors contained in investigational medicinal products for human use" er i tråd med kravene til vurdering av helse og miljørisiko. VKM har ikke vurdert skjema etter juridiske krav, men har gjort en vurdering av om innholdet i søknadskjema er tilstrekkelig for å kunne utføre en helse- og miljørisikovurdering av virus vektorer som skal benyttes i kliniske studier på mennesker. Alle deler av skjema er vurdert i tabellen under.

Tabell. VKMs vurdering av søknadsskjemaet: «Common application form for viral vectors contained in investigational medicinal products for human use".

VKM har vurdert skjemaet fra del 2 i tråd med oppdraget, men hele skjemaet er vist for leservennlighet.

<table>
<tr><th>Del av skjema</th><th>Innhold i skjema</th></tr>
<tr><td>Forside</td><td>Common application form for viral vectors contained in investigational medicinal products for human use[1]

Note 1: This application form can be used for submissions in the following jurisdictions: Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, the Netherlands, Romania, Slovenia, and Spain.

Note 2: The application form must be accompanied by the SNIF (summary notification information format for notifications concerning the deliberate release into the environment of genetically modified organisms for purposes other than for placing on the market)[2] in the case of submissions that are made under Directive 2001/18/EC.

<table>
<tr><th>Document history</th><th>Publication date</th><th>Description of main changes</th></tr>
<tr><td>Version 1</td><td>1 October 2019</td><td></td></tr>
<tr><td>Version 2</td><td>2 December 2020</td><td>Endorsement by additional Member States (LT, SI)</td></tr>
</table>
[1]This document has not been adopted by the European Commission and, therefore, it does not contain the official position of the European Commission.

[2]Council Decision 2002/813/EC establishing, pursuant to Directive 2001/18/EC of the European Parliament and of the Council, the summary notification information format for notifications concerning the deliberate release into the environment of genetically modified organisms for purposes other than for placing on the market (OJ L 280,18.10.2002, p.62).</td></tr>
</table>

1. Introduction	Clinical trials conducted in the EU with investigational medicinal products that contain or consist of genetically modified organisms ("GMOs"[3]) must comply with the legislation governing the authorization of clinical trials.[4] Clinical trials with medicinal products that contain or consist of GMOs must also comply with applicable requirements under Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms[5]("deliberate release framework") and/or under Directive 2009/41/EC on the contained use of genetically modified micro-organisms ("contained use framework").[6] This application form implements the requirements of the Directive 2009/41/EC and of the Directive 2001/18/EC, as adapted to the specific characteristics of viral vectors contained in investigational medicinal products for human use. This is an application form for medicinal products for human use that contain or consist of viral vectors (hereafter referred to as "clinical vectors"). Specific application forms developed for certain category of medicinal products prevail over this application. For example, developers of CAR T-cells should use the *common application form for clinical research with human cells genetically modified by means of retro/lentiviral vector*. Likewise, developers of AAVs should use the *common application form for investigational medicinal products for human use that contain or consist of AAV vectors*. Finally, in case the application concerns an investigational medicinal product that has already been granted a marketing authorisation, the *submission form for use in case of clinical trials with authorised medicinal products* should be used.[7] The application form has been endorsed by Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, the Netherlands, Romania, Slovenia and Spain and may be used for submissions to these Member States. [3]Throughout this document, the term "GMO" should be understood as covering both genetically modified organisms as defined under Article 2(2) of Directive 2001/18/EC, and genetically modified micro-organisms within the meaning of Article 2(b) of Directive 2009/41/EC. [4]Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use and repealing Directive 2001/20/EC, (OJ L158, 27.5.2014, p.1). Until the Regulation applies, Directive 2001/20/EC is applicable (Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, OJ L121,1.5.2001, p.34). [5]Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC (OJ L 106, 17.4.2001, p. 1). [6]Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms (OJ L 125, 21.5.2009, p. 75). [7]The specific application/submission forms referred to in this paragraph are only applicable in the countries that have endorsed them.
2. Explanatory notes	The common application form is without prejudice to consultation requirements that exist under Directive 2001/18/EC. In addition, certain national requirements may need to be considered by developers of medicinal products before they submit the application form to the relevant competent authorities:

	Austria: Applicants should send separate submissions in case there are multiple sites concerned in Austria (including clinical premises, laboratories in which activities with GMOs are carried out, locations of storage of the investigational medicinal product and location of storage of samples from clinical trial subjects that contain GMOs). Further information is available at: https://www.sozialministerium.at/site/Gesundheit/Gentechnik/Rechtsvorschriften_in_Oesterreich/ **Belgium:** The common application form should be part of a biosafety dossier submitted by each of the clinical sites where the investigational medicinal product will be administered. However, one person (e.g. the sponsor) can be empowered by the concerned sites to submit all the necessary notifications, provided that the person responsible for the activity is clearly indicated in the form. More information on procedural requirements and forms for the three regions is available at: https://www.biosafety.be/content/contained-use-gmos-andor-pathogenic-organisms-notification-procedures. **Czech Republic:** Each clinical site as well as other institutions where the activities with GMOs will take place (e.g. laboratories that are not premises of one of the clinical sites) should submit a separate notification for deliberate release or for contained use, as appropriate. However, one person (e.g. the sponsor) can be empowered by the concerned sites/institutions to submit all the necessary notifications. **France:** For investigational medicinal products that are assessed under the contained use framework, applicants should send separate submissions in case there are multiple sites concerned in France. **Italy:** For investigational medicinal products that are assessed under the contained use framework, each clinical site (including clinical premises, laboratories in which activities with GMOs are carried out, locations of storage of the investigational medicinal product and location of storage of samples from clinical trial subjects that contain GMOs) should submit a separate notification. However, one person (e.g. the sponsor) can be empowered by the concerned sites/institutions to submit all the necessary notifications. It is stressed that, in case the submission is made by a third party on behalf of the site, the responsibilities of the site holders and users concerned (as set out under Legislative Decree n. 206/2001) remain unchanged. **The Netherlands:** More information on national procedural requirements and forms is available at: https://www.loketgentherapie.nl/en/viral-vectors
SECTION 1 –ADMINISTRATIVE INFORMATION	
1.1. Identification of the applicant.	Organisation Name: Address Details: Contact person:

	Telephone No: Email Address:	
1.2. Identification of the sponsor (to the extent that is different from the applicant).	Organisation Name: Address Details: Contact person: Telephone No: Email Address:	
1.3. Identification of the manufacturer of the clinical vector.	Organisation Name: Manufacturing location:	
SECTION 2 – INFORMATION RELATING TO THE INVESTIGATIONAL MEDICINAL PRODUCT		
A. Virus from which the clinical vector was derived (parental virus)		
A.1. Characterisation		**VKMs vurdering**
2.1. Which virus was used as the parental virus in the construction of the clinical vector?	Scientific name: Strain and isolate: Other names (e.g. commercial name): Biosafety classification[8]: Parental virus attenuated: Yes No [8]Explain if the classification varies between different territories in which the clinical trial will take place.	VKM vurderer at en detaljert beskrivelse av foreldreviruset, dets egenskaper og inneslutningsnivå er tilstrekkelig informasjon for å vurdere sikkerhet rundt produksjon av virus-vektor, samt for å kunne sammenligne egenskaper mellom foreldrevirus og virusvektor. Egenskapene til foreldreviruset kan variere med stammen og et attenuert foreldrevirus vil kunne gi lavere miljørisiko enn et som ikke er attenuert.
2.2. Phenotypic and Genetic Markers.	*Briefly describe the most relevant phenotypic and genetic markers of the parental virus, including information on the viral genome size and the packaging limit of the parental virus.*	VKM vurderer informasjon om hvor mye foreldreviruset kan pakke, størrelse av genomet og andre relevante markører som tilstrekkelig. Informasjonen har betydning for hvor stort insert virus-vektor kan frakte, begrenses naturlig av genomstørrelsen til foreldreviruset. For familen rhabdovirus vil ekstragener medføre at viruspartikklen «forlenges»og det er ikkeplassmangel som begrenser størrelse på insert. VKM vurderer at andre relevante markører som kan være relevante å nevne er: virulensfaktorer, evne til latens, type og organisering av arvematerialet, og regulatoriske elementer for replikasjon.
2.3. What is the host range of the parental virus?	*Describe the hosts in which the parental virus naturally occurs, also including hosts that serve as a reservoir. For each possible host, indicate the tissue and cell tropism.*	VKM vurderer at informasjonen om vertsspekteret til foreldreviruset vil være tilstrekkelig.

	If natural hosts of the parental virus include humans, provide available information about the seroprevalence in the EU.	Bruk av et foreldrevirus som også forekommer naturlig som villtypevirus og har et bredt vertsspekter, og bred celle- og vevstropisme vil potensielt kunne gi større miljørisiko, enn et foreldrevirus som ikke forekommer naturlig som villtypevirus. Celle- og vevstropisme har betydning for utskillelse. Seroprevalens vil kunne gi informasjon om forekomsten av antistoffer mot foreldreviruset i befolkningen dersom foreldreviruset forekommer naturlig som villtypevirus. Informasjonen kan brukes til å vurdere risiko for spredning i miljø ved eventuell revertering av virus-vektor, dersom antistoffene i befolkningen er korrelert med beskyttelse mot infeksjon. Høy forekomst av beskyttende antistoffer vil for eksempel kunne gi mindre risiko for spredning.
2.4. Zoonotic potential of the parentalvirus.[9]	*If humans are not natural hosts of the parental virus, provide information on the zoonotic potential of the parental virus. Describe also the natural geographic distribution of the parental virus and indicate if the parental virus is endemic in the EU.* [9]This Section needs not be filled in case of replication incompetent clinical viral vectors.	VKM vurderer informasjonen som tilstrekkelig for å vurdere det zoonotiske potensiale til foreldreviruset, det vil si dets evne til å smitte til andre mennesker eller dyr ved eventuell revertering av virus-vektor. Den naturlige utbredelsen til foreldreviruset (f.eks. dersom det er likt villtypevirus) kan påvirke sannsynlighet for at virus-vektor rekombinerer med foreldreviruset.
2.5. Replication properties of the parental virus.	*Provide information about the replication of the parental virus. Indicate where replication takes place (cell nucleus, cytoplasma). Is the parental virus capable of establishing latency in the natural host? What are the sequence elements involved in the reactivation process? Provide also any available information on the potential for homologous/non-homologous genomic recombination occurring in nature between viral genomes of the parental virus and related strains or members of the same viral (sub)family.*	VKM vurderer denne informasjonen om foreldrevirusets replikasjon som viktig og tilstrekkelig. Egenskapene er relevante for å vurdere risiko for at det dannes replikasjonskomptente virus og evne til latens. Bruk av et foreldrevirus som ofte rekombinerer naturlig vil kunne være mer forbundet med større risiko, sammenlignet med et foreldrevirus som i mindre grad har denne egenskapen.
A.2. Pathogenicity		
2.6. What are the pathogenic properties of the parental virus and what are the available	*Describe any pathogenic properties of the parental virus. Where relevant, provide information on pathogenic properties of the parental virus in vulnerable groups such as immunosuppressed individuals, pregnant women and small children. Describe the symptoms caused by the parental virus.*	Relevant. Det er en teoretisk mulighet at vektoren ved rekombinering kan revertere tilbake til foreldreviruset dersom det er et passende donorvirus til stede i cellene som er blitt transdusert med virus- vektoren.

treatment methods?	*Indicate also if therapeutic/prophylactic treatments exist to treat/prevent such an infection.*	Derfor er det relevant å oppgi patogene egenskaper for foreldreviruset.
2.7. Provide relevant data on attenuation and biological restrictions of the parental virus.	*If the parental virus is an attenuated/restricted virus, the basis for attenuation/restriction should be described. Describe the conditions (steps)needed for reversion of the attenuation/restriction and the factors that may affect reversion.*	Her skal man oppgi informasjon om forskjeller mellom foreldreviruset og villtypevarianten av det viruset som er opphav til vektoren og hva som skal til for at revertering av foreldrevirus til villtypevirus. Det kan være relevant dersom foreldre- og villtypevirus er relativt like.
A.3. Ability to colonise		
2.8. What are the transmission routes of the parental virus?	*Describe possible transmission routes of the virus. Provide information on viral shedding including asymptomatic shedding of the parental virus. In the case of vector-borne viruses (e.g. arbo viruses), indicate the geographic location of the vector.*	Relevant. Utskillelse av foreldrevirus vil være retningsgivende for hvordan man tror virusvektor eventuelt vil skilles ut. Dersom virus-vektor er infeksiøst, vil det være interessant å kjenne smitteveier for foreldreviruset.
2.9. Can the parental virus survive outside the host?	*Describe all survival options and the survival time of the parental virus under optimal environmental conditions, and describe the factors that may be of influence.*	Relevant. Hvor lenge et foreldrevirus er infeksiøst, hvilke betingelser som influerer på dette er relevant for å vurdere miljørisiko som virus-vektor kan utgjøre. Det kan også være retningsgivende for valg av desinfeksjon ved kontaminasjon / uhell med vektor.
B. Genetic modification and manufacturing of the clinical vector		
2.10. Provide a brief description of the manufacturing process of the clinical vector.	*Answer this question preferably by using a diagram that describes the various production steps.* *[7]When using plasmids for the manufacturing of the clinical vector, clear maps of the plasmids showing all the constituent parts of the vector should be provided (i.e. in addition to the "transgene plasmid", all other plasmids such as helper, packaging and pseudotyping plasmids should be described). Explain if there are overlapping sequences in the plasmids.* *Confidential information should be provided in an annex, together with the reasons why it is considered confidential. The Section of the application form to which the information refers should be clearly identified. When confidentially is claimed, a summary that can be made public should be provided in this section.*	VKM vurderer at en beskrivelse av arbeidet med vektoren pluss et diagram som viser hele produksjonsprosessen (plasmider, bakteriestammer, cellelinjer) og en oversikt over alle genetiske endringer som er gjort plasmidene som brukes vil være tilstrekkelig til å vurdere hvordan preparatet er satt sammen og produsert. Introduksjon av mutasjoner i vektoren bør også forklares.
2.11. Describe the characteristics of the cell lines in which the clinical	*The characteristics of all cell lines used and eventual modifications of the cell genome should be explained. Describe the cell types concerned as well as their origin (e.g. human kidney, epithelial cells). The possibility of the genetic material in the cells/cell lines*	VKM vurderer at dette er tilstrekkelig for å vurdere om produksjonsmetoden øker risiko for komplementering eller rekombinasjon. Informasjon om cellelinjenes opprinnelse og

vector is produced. Also indicate which of the genetic components of the cell could possibly cause complementation or recombination.	*causing a certain interaction with the clinical vector, such as by complementation or recombination should be discussed.* *Explain if there is a risk of clinical vector modification by trans-complementing sequences. Provide also a description of the identity of these sequences. This can be done on the basis of bio-informatic analysis, such as sequence analysis, alignments or phylogenetic analysis.* *Confidential information should be provided in an annex, together with the reasons why it is considered confidential. The Section of the application form to which the information refers should be clearly identified. When confidentially is claimed, a summary that can be made public should be provided in this section.*	eventuelle genetiske endringer vil danne grunnlag for vurdering av risiko.
2.12. Contaminating replication-competent virus.	*For replication-deficient and conditionally replication-competent clinical vectors, strategies to avoid the generation of replication-competent virus (RCV) should be described. Test methods for detection of replication-competent virus should be described, including information on the specificity and sensitivity thereof. Data from RCV testing at different manufacturing steps should be provided (e.g. virus seed bank, final product). Release criteria with regard to RCV testing should be specified.* *Confidential information should be provided in an annex, together with the reasons why it is considered confidential. The Section of the application form to which the information refers should be clearly identified. When confidentially is claimed, a summary that can be made public should be provided in this section.*	VKM vurderer at de beskrevne tiltak for å unngå kontaminering av produktet med replikasjonskompetene virus er tilstrekkelig. Cellelinjen som brukes for vektorproduksjon kontrolleres for tilstedeværelse av et bredt register av mulige kontaminanter: bakterier, mykoplasmer og en lang rekke virus som kan tenkes å etablere persistente infeksjoner i cellelinjen.
C. Clinical vector		
2.13. Provide a diagram ('map') of the clinical vector.	*Confidential information should be provided in an annex, together with the reasons why it is considered confidential. The Section of the application form to which the information refers should be clearly identified. When confidentially is claimed, a summary that can be made public should be provided in this section*	VKM vurderer at et slikt diagram (plasmidkart) er tilstrekkelig for å få oversikt over vektorens elementer.
2.14. Molecular characterisation of the clinical vector(s).	*Provide the annotated sequence of the complete genome (i.e. indicate the location of the sequences encoding the transgene expression cassette(s) and its regulatory elements). As a minimum, the sequence of*	VKM vurderer at en molekylær karakterisering av vektoren (fullstendig RNA eller DNA sekvens) med tilhørende forklaring

	the elements that could affect the replication ability, host range, tropism, ability to survive outside the host, route of transmission or pathogenic potential of the clinical vector should be provided. *Describe in what way the clinical vector deviates from the parental virus at the level of molecular characterisation.* *Available data supporting genetic stability of the clinical vector should be provided. Deviations should be discussed, in particular the biological significance thereof.* *Confidential information should be provided in an annex, together with the reasons why it is considered confidential. The Section of the application form to which the information refers should be clearly identified. When confidentially is claimed, a summary that can be made public should be provided in this section.*	(annotering) er tilstrekkelig for en karakterisering av vektoren. I tillegg bør det inkluderes en tabell som viser alle endringer vektoren sammenlignet med den naturlige forekommende sekvensen (villtypeviruset). En sammenligning av sekvensene fra villtype virus og vektoren ("alignment") bør også inkluderes. Eventuell konfidensiell informasjon (produktkritiske mutasjoner) kan flyttes til et upublisert tilleggsdokument og kun kommenteres i hoveddokumentet.
2.15. Describe the coding genes and the regulatory sequences present in the clinical vector backbone and in the DNA inserted.	*A full description must be provided of the inserted or deleted genetic material, also discussing the functions of the sequences, for example:* *-Expression cassette, including promoter, terminator, and enhancer sequences.* *-Transgene: e.g. is the expressed product toxic or otherwise harmful to humans (other than the clinical trial subject) or other hosts? Does the transgene provide an advantage for replication/ survival of the clinical vector (vis-à-vis parental virus) or alter the transmission route?* *-Whether the DNA inserted into the clinical vector contains elements of which the origin or function is unknown.* *-Whether the clinical vector contains elements that are not specifically intended for the therapeutic functions.* *Confidential information should be provided in an annex, together with the reasons why it is considered confidential. The Section of the application form to which the information refers should be clearly identified. When confidentially is claimed, a*	VKM vurderer at en beskrivelse av genene som uttrykkes (f.eks om proteinene er toksiske for andre arter eller gir vektoren mer effektiv replikasjon) via virus-vektoren og hvordan disse er regulert er tilstrekkelig. Eventuell konfidensiell informasjon (produktkritiske mutasjoner) kan flyttes til et upublisert tilleggsdokument og kun kommenteres i hoveddokumentet.

	summary that can be made public should be provided in this section.	
2.16. Differences between the biological profile of the clinical vector and the parental virus.	*Indicate whether the clinical vector particles are pseudotyped and whether the envelope is provided in trans.* *Explain differences that exist between the clinical vector and the parental virus regarding:* *-Host range, including host specificity and the tissue and cell tropism.* *-Transmission route.* *-Pathogenic properties. Where relevant, consider potential effects in common population and in vulnerable groups such as immunosuppressed individuals, pregnant women, small children, or any other group with a higher risk.* *-Ability to survive outside the host. If available, provide data on the loss of infectivity of the clinical vector on different materials or in liquids (e.g. waste water).* *Confidential information should be provided in an annex, together with the reasons why it is considered confidential. The Section of the application form to which the information refers should be clearly identified. When confidentially is claimed, a summary that can be made public should be provided in this section.*	VKM vurderer informasjonen som beskriver biologiske forskjeller mellom klinisk vektor og foreldrevirus som viktig og tilstrekkelig. Pseudotyping av virus-vektor vil kunne påvirke vertsspekter, celle- og vevstropisme for vektoren, slik at dette blir mer kontrollert og forhindrer infeksjon av verter og celler som ikke er mål for behandlingen. Gener som koder for kappeproteiner kan gis i trans (på separat plasmid) og gjøres blant annet for lenti-virusvektorer for å redusere risiko for dannelse av replikasjonskompenent virus.
2.17. Potential for recombination with the parental virus in vivo and description of potential recombinants.	*Discuss the potential for homologous recombination in vivo and describe all recombinants that might be generated by homologous recombination with e.g. the parental virus. Discuss the potential biological (including pathogenic) effects of any possible recombination for the population (including for vulnerable groups). Indicate whether the recombinants described have been monitored and detected in previous experiments or after administration to humans.*	VKM vurderer informasjonen som viktig og tilstrekkelig for å kunne beskrive sannsynligheten for at klinisk vektor rekombinerer med foreldrevirus i pasienten samt konsekvensen dersom dette skjer.
2.18. Biodistribution and shedding.	*Detailed data on vector shedding (including information on the administered dose, the route of administration, and –where available-immune status of the treated subjects) from previous clinical trials with the clinical vector should be provided. Where available and if relevant for the environmental risk*	VKM vurderer informasjonen som viktig og tilstrekkelig for å kunne vurdere biodistribusjon i studiedeltakerne og risiko for utskillelse til miljø, både når det gjelder mengde og varighet.

	assessment, biodistribution data should be provided. If there is no prior clinical experience with the same clinical vector, the potential for shedding should be discussed based on non-clinical data and/or clinical experience from related clinical vectors. If the applicant relies on data from related clinical vectors, the relevance of the data to the product that is the object of this application should be explained considering, in particular, the dose and route of administration. When shedding occurs, the estimated duration should be specified. The methods used for detection of viral shedding including information on the specificity (including ability to detect revertants) and sensitivity thereof should be provided.	
SECTION 3 – INFORMATION RELATING TO THE CLINICAL TRIAL		
3.1. General information about the clinical trial.	EudraCT-number (where available): Deliberate release reference number (where available and applicable): Title of the clinical trial: Name of principal investigator: *This information may be provided in the annex with confidential information.* Objective of the study: Intended start and end date: Number of trial subjects that will take part in the study: Indicate if an application related to the same investigational medicinal product has been submitted -or is planned to be submitted-to other EEA Member States. In the affirmative, identify the countries concerned:	VKM vurderer dette som relevant informasjon Det er viktig å få vite om eventuelle andre kliniske studier på samme legemiddel, det være seg andre klinisk studier med annet design eller på andre indikasjoner. Et legemiddel (medicinal product) kan ha ulik formulering og styrke, Kunnskapen om eventuell annen fremtidig bruk vil kunne gi en pekepinn på for eksempel antall pasienter som vil være brukere av produktet
3.2. Intended location(s) of the study.	The applicant should provide information about the clinical sites located in the country of submission of the application. In some jurisdictions, the following additional information should be provided: • the location(s) of laboratories (in the country of submission) in which activities with the GMO are carried out under the framework of the clinical trial application should be stated.[10] • information about the location where the investigational medicinal product is stored (to the extent that the location is in the country of submission but outside the	VKM vurderer at tilleggsinformasjon om **hvor** studien skal utføres bør være tilgjengelig VKM vurderer at tilleggsinformasjon om **hvor** produktet skal lagres (dette kan være generell informasjon, f. eks sykehusapotek) bør være tilgengelig og at denne informasjonen er relevant for miljørisikovurdering.

	clinical site).[11] information about the location where patient's samples that contain GMO's are stored (to the extent that the location is in the country of submission but outside the clinical site).[12] Organisation Name: Address Details: Contact person: Telephone No: Email Address: Planned activities: Containment level: Name and contact details of the responsible person*13*: Organisation Name: Address Details: Contact person: Telephone No: Email Address: Planned activities: Containment level: Name and contact details of the responsible person: (Applicant should complete as many tables as necessary) [10]Information about the location of laboratories is required for applications submitted to Austria ,Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, and Spain. In case of submissions to these jurisdictions, fill in the relevant table for laboratories that conduct specialised analysis referred in the protocol of the clinical trial only; laboratories that perform standard laboratory diagnostics analysis need not be listed. [11]This information should be provided for applications submitted to Croatia, Germany, Ireland and Spain. This information should be provided for applications submitted to Belgium, Czech Republic, and Finland, unless there is a contained use notification covering the storage of the product. [12]This information should be provided for applications submitted to Croatia, Ireland, and Germany. For applications submitted to Belgium, Czech Republic and Finland, this information should be provided if the patient samples contain replicative	

	and infective viruses (unless there is a contained use notification covering the storage). [13]The responsible person is either the person responsible for supervision and safety as provided for under V of Directive 2009/41/EC, or the responsible scientist as provided for under Annex IIIA of Directive 2001/18/EC.	
3.3. Storage of the clinical vector at the clinical site.	*The applicant should provide information about the storage location, conditions of storage (including restrictions of access), and the maximal storage duration.*[14] [14]*In case of applications submitted to Austria, Belgium, Croatia, Czech Republic, Finland, France, Ireland, Italy, the Netherlands and Spain, the applicant should specify if the dose is being prepared in the hospital pharmacy. If the clinical dose is prepared at a location other than the hospital pharmacy, this should be explained.*	VKM vurderer at dette antakelig vil gi god nok informasjon. Noen land ønsker I tillegg å vite hvor dosen skal prepareres til pasienten. Sykehusapotek blir nevnt her spesifikt. Dette er fordi de fleste sykehusapotek har kompetanse og spesialutstyr/rom som kan sikre en forsvarlig preparering av ferdig produkt til pasient. VKM vurderer at en bør ha med slik informasjon ved klinisk utprøvninger også i Norge. Det vil sikre at legemiddelet håndteres etter prinsipper om "Good Manufacturing Practice" for medicines og øke sikkerhet med hensyn på lagring, håndtering og søl.
3.4. Logistics for on-site transportation of the clinical vector.	*The applicant should provide information about the logistics for in-house transportation (i.e. transfer of the clinical vector from storage to the administration site and –where applicable-site where dose is prepared). The applicant should provide information about the characteristics of the containers used addressing also disinfection procedures applied and labelling of the containers.*	VKM vurderer at denne informasjonen er relevant og tilstrekkelig for miljørisikovurdering.
3.5. Information about reconstitution, finished medicinal product and administration to patients.	Reconstitution (where applicable, summarise reconstitution steps): Pharmaceutical form and strength: Mode of administration: Information on dosing and administration schedule (in case of repeated dosing): Information on concomitant medication that may affect the shedding of the clinical vector/ environmental risks (e.g. administration of laxatives, administration of a medicinal product that could enhance the replication activity of the clinical vector, administration of a plasmid-based medicinal product):	VKM vurderer at denne informasjonen er relevant og tilstrekkelig for miljørisikovurdering.
3.6. Measures to prevent dissemination into the environment.		VKM vurderer at denne informasjonen er relevant og tilstrekkelig for miljørisikovurdering.

a)	Control measures during reconstitution (if applicable), handling and administration.	VKM vurderer at denne informasjonen er relevant og tilstrekkelig for miljørisikovurdering.
b)	Personal protective equipment	VKM vurderer at denne informasjonen er relevant og tilstrekkelig for miljørisikovurdering.
c)	Decontamination/cleaning measures after administration or in the case of accidental spilling (i.e.decontamination /cleaning measures of potentially contaminated materials, surfaces and areas). In addition, the disinfection procedures applied should be justified by providing evidence that the chosen method is sufficiently active against the clinical vector.	VKM vurderer at denne informasjonen er relevant og tilstrekkelig for miljørisikovurdering.
d)	Elimination or inactivation of left-overs of the finished product at the end of the clinical trial.	VKM vurderer at denne informasjonen er relevant og tilstrekkelig for miljørisikovurdering.
e)	Waste treatment (including also –where applicable- decontamination and disposal of potentially contaminated waste that accumulates outside the clinical trial site). Where applicable, identify also the company responsible for waste management.	VKM vurderer at denne informasjonen er relevant og tilstrekkelig for miljørisikovurdering.
f)	Are there exclusion criteria applied to the enrolment of patients in the clinical trial to address environmental risks? Are the treated patients subject to restrictions after administration of the product?	VKM vurderer at denne informasjonen er relevant og tilstrekkelig for miljørisikovurdering.
g)	Recommendations given to clinical trial subjects to prevent dissemination.	VKM vurderer at denne informasjonen er relevant og tilstrekkelig for miljørisikovurdering.
h)	Recommendations on donation of blood/cells/tissues/organs by the clinical trial subject.	VKM vurderer at denne informasjonen er relevant og tilstrekkelig for miljørisikovurdering.
i)	Other measures.	Her kunne man tenke seg at en vurderer om hvordan en håndterer eventuelle kroppsvæsker fra pasient. For eksempel oppkast, bleier etc (slike tiltak eksemplifiseres i GMO-interplay dokument om onkolytiske virus). Det vil gjøre at utskillelse av virus-vektor håndteres på en slik måte at sikkerhet ved håndtering og søl er ivaretatt.
3.7. Sampling and further analyses of samples from study subjects.	This Section should be filled in where samples that may contain GMOs are being taken from patients in the context of the clinical trial land the application is submitted to the following jurisdictions: Croatia, Czech Republic, Denmark, Germany, Ireland, Italy, Hungary, the Netherlands and Spain.	VKM vurderer at denne informasjonen er relevant og tilstrekkelig for miljørisikovurdering.

a)	Describe how samples will be handled/stored/transported. To the extent that handling/ storage and transport of samples are treated under same procedures as the clinical vector, cross-reference can be made as appropriate.	VKM vurderer at denne informasjonen er relevant og tilstrekkelig for miljørisikovurdering.
b)	Indicate whether and at which time points samples that may contain the administered clinical vector are taken from study subjects.	VKM vurderer at denne informasjonen er relevant og tilstrekkelig for miljørisikovurdering.
c)	If samples are stored at the clinical site, describe storage location and storage conditions.	VKM vurderer at denne informasjonen er relevant og tilstrekkelig for miljørisikovurdering.
d)	Explain if there is any non-routine[15] testing of the samples and indicate whether the clinical vector is generated de novo during the testing. [15]Standard clinical care tests as well as tests required to fulfil long-term follow-up of clinical trial subjects need not be mentioned.	VKM vurderer at denne informasjonen er relevant og tilstrekkelig for miljørisikovurdering.
3.8. Emergency response plans.[16]	Emergency response plans for accidental self-administration during handling or administering the clinical vector: Emergency response plans for accidental release into the environment of the clinical vector: [16]In the case of applications submitted in Austria, Finland, France and Ireland, information on emergency response plans is only required if the clinical vector has been classified as BSL 3 or 4.Inthe case of submissions to Italy, the emergency response plan does not need to be provided; an emergency response plan may, however, be requested by the authorities if appropriate.	VKM vurderer at denne informasjonen er relevant og tilstrekkelig for miljørisikovurdering.
SECTION 4 – OTHER DATA REQUIREMENTS		
4.1. Plan of the site(s) concerned	*Applicants should provide a copy of the plan of the site where the clinical trial takes place if the application is submitted to the following jurisdictions: Austria, Belgium, Croatia, Czech Republic, Finland, France, Hungary, Ireland and Italy.*	
4.2. Other information	***Submissions to Austria**:* *In addition to the plan of the site, a description of the location of the autoclave should be provided –as appropriate-as part of the description of the measures to prevent dissemination into the environment referred in Section 3.6 (d) and (e).* ***Submissions to Belgium:***	I denne delen av skjemaet kan søkeren legge inn tilleggsinformasjon hvis det er krevet av landet hvor utprøvningen skal foregå. Tyskland krever informasjon om bruken av desinfeksjonsmidler og avfallshåndtering. VKM mener at dette kan være nyttig informasjon, men anser at dette dekkes av punktene 3.6 a) – d).

	In addition to the plan of the site, a description of the location of the autoclave and the biosafety cabinet should be provided –as appropriate-as part of the description of the measures to prevent dissemination into the environment referred in Section 3.6 (d) and (e). The applicant is also asked to provide an overview (table) of the rooms involved in the CT activity by indicating for each of those the number of the room, the type of handling carried out (e.g. storage, administration of the IMP, reconstitution of the IMP) and the containment level. ***Submissions to Czech Republic:*** *In addition to the plan of the site, a description of the location of the autoclave should be provided –as appropriate-as part of the description of the measures to prevent dissemination into the environment referred in Section 3.6 (d) and (e).* ***Submissions to France:*** *The plan of the site should indicate clearly the location of a PSMIIor an equivalent device.* ***Submissions to Germany:*** • *The applicant is not required to provide further information in Section 3(6)(c) if he/she confirms that the disinfectant and decontamination procedure are included in the list of the Robert Koch Institute of currently approved disinfectants and disinfectant procedures or the VAH (Verbund für Angewandte Hygiene e.V) list of disinfectants* • *The applicant should explain fleft-overs are stored at the clinical site and, if in the affirmative, for how long as part of the information submitted in Section 3(6)(d)* • *The applicant should provide the following information on waste treatment in Section 3(6)(e):—Whether and for how long the waste will be stored (or frequency of waste disposal),—Storage location, —Logistics for on-site transportation of the waste (similar as asked for the clinical vector in Section 3.4), and—In case of chemical decontamination whether the chosen disinfectant and method is sufficiently active against the clinical vector (similar as in Section 3.6.c)*	VKM legger til grunn at de som utfører denne type kliniske forsøk er kjent med plassering av autoklaver, sikkerhetsbenker o.l. der hvor preparatet skal bli brukt, tilpasset de nasjonale krav for bruk av GMO preparater I klinisk utprøvning.

	• *If samples are stored at the clinical site, the maximum duration of the storage should be stated in Section 3.7(c).* ***Submissions to Ireland:*** • *In addition to the plan of the site, a description of the location of the autoclave should be provided –as appropriate-as part of the description of the measures to prevent dissemination into the environment referred in Section 3.6 (d) and (e).* • *If samples are stored at the clinical site, the maximum duration of the storage should be stated in Section 3.7 (c).* ***Submissions to Italy:*** *In addition to the plan of the site, a description of the location of the autoclave should be provided –as appropriate-as part of the description of the measures to prevent dissemination into the environment referred in Section 3.6 (d) and (e). If the manufacturer of the clinical vector is located in Italy, the authorisation issued to the premises should be declared in Section 1.3.type of handling carried out (e.g. storage, administration of the IMP, reconstitution of the IMP) and the containment level.*	
SECTION 5 – ENVIRONMENTAL RISK ASSESSMENT *This Section should be filled in for submissions under Directive 2001/18/EC.*[17] [17]*In the case of applications submitted to Italy, this Section should always be filled in.*		
A. Risk analysis *In filling this Section, applicants may refer to relevant literature data and results from earlier preclinical and/or clinical studies.*		
A.1. *Risks to healthcare professionals and/or close contacts of the clinical trial subject (including vulnerable groups)*		
5.1. Hazard identification:	*Provide a list of the potential adverse effects (e.g. immune reaction, integration in the genome of the exposed cells, adverse effects linked to the expression of the therapeutic gene, etc.) if transmission of the clinical vector or potential revertants to thirds - including vulnerable groups-occurs through shedding (as described in Section 2.18).*	VKM vurderer at denne informasjonen er relevant og tilstrekkelig. Informasjonen er viktig for å lage gode retningslinjer for beskyttelse av de som tilrettelegger og håndterer produktet og pasienten under studien
5.2. Hazard characterisation:	*Provide an estimate of the magnitude of each of the identified potential adverse effects (it should be assumed that each of the hazards will occur). Where a quantitative estimation is not possible, a category ("high", "moderate", "low" or "negligible") should be assigned.*	VKM vurderer at denne informasjonen er relevant og tilstrekkelig.
5.3. Exposure characterisation:	*Provide an estimate of the likelihood (probability) that each of the identified hazards will occur. Where a quantitative estimation is not possible, a category*	Her skal søkeren karakterisere sannsynligheten for uønskede hendelser ved

	("high", "moderate", "low" or "negligible") should be assigned.	bruk av preparatet. VKM mener at dette er relevant og tilstrekkelig informasjon. Det bør medfølge en definisjon eller en vurdering fra søker om hva som legges i begrepene ("high", "moderate", "low" or "negligible
5.4. Risk characterisation:	*Considering the magnitude of each of the effects identified and the likelihood of their occurrence, characterise the risk. Where a quantitative estimation is not possible, a category ("high", "moderate", "low" or "negligible") should be assigned.*	Her skal søkeren karakterisere risiko for skade på personell eller nære kontakter til pasienten ved bruk av preparatet. Dette er en nødvendig del av karakteriseringen og VKM vurderer dette som relevant og tilstrekkelig informasjon
5.5. Risk management strategies:	*The applicant should explain measures implemented to reduce the potential risks to thirds and/or the environment associated with the clinical use of the clinical vector. This includes -but is not limited to-the measures implemented to prevent the risks of accidental transfer during reconstitution, handling, administration of the product, or during manipulation of patient's samples (after administration of the clinical vector). The applicant should also explain the recommendations that will be provided to the clinical trial subject and/or close contacts to prevent dissemination/accidental contamination. Finally, the applicant should consider if clinical trial subjects should be prevented from donating blood/cells/ tissues/ organs after being administered the clinical vector. This information should be listed in Section 3.6.*	VKM vurderer at denne informasjonen er viktig og særs relevant med tanke på at det er nye og ukjente substanser som prøves ut. Det er ryddig at dette beskrives så nøye. VKM vurderer at informasjonen er tilstrekkelig.
A.2. Risks to the environment		
5.6. Hazard identification:	*Provide a list of the potential adverse effects. As appropriate, consider specific environmental conditions that may affect the survival, replication or ability to colonise (wind, water, soil, temperatures, pH, etc).*	VKM vurderer dette som tilstrekkelig. Se også svar til punktene 2.9 og 2,12.
5.7. Hazard characterisation:	*Provide an estimate of the magnitude of each of the identified potential adverse effects (it should be assumed that each of the hazards will occur). Where a quantitative estimation is not possible, a category ("high", "moderate", "low" or "negligible") should be assigned.*	VKM vurderer dette som tilstrekkelig for vurdering av konsekvens.
5.8. Exposure characterisation:	*Provide an estimate of the likelihood (probability) that each of the identified hazards will occur. Where a quantitative estimation is not possible, a category ("high", "moderate", "low" or "negligible") should be assigned.*	VKM vurderer dette som tilstrekkelig for vurdering av sannsynlighet.
5.9. Risk characterisation:	*Considering the magnitude of each of the effects identified and the likelihood of their occurrence, characterise the risk. Where a quantitative estimation*	VKM vurderer dette som tilstrekkelig for vurdering av risiko.

	is not possible, a category ("high", "moderate", "low" or "negligible") should be assigned.	
5.10. Risk management strategies:	*The applicant should implement adequate measures to prevent dissemination into the environment. These should be listed in Section 3.6.*	VKM vurderer dette som tilstrekkelig for å kunne vurdere risikoreduserende tiltak.
A.3. Overall risk evaluation and conclusions		
5.11.	*Evaluate the overall risk of the clinical vector for humans (healthcare professionals and close contacts of the patient) and the environment considering, as applicable, the risk management strategies described in Section 3.6.*	VKM anser det som nødvendig å gi en helhetlig miljørisikovurdering basert på opplysninger som har kommet fram i punktene over.

2.*2 Dette søknadsskjemaet for virusvektorer kommer ikke med en ferdigskrevet ERA, men dekker søknadsskjemaets punkter om miljørisikovurdering etter VKMs vurdering alle deler av en ERA?*

Direktoratet ser at spørsmål 1 og 2 muligens vil være overlappende i en viss grad, men ber VKM i svaret på spørsmål 2 fokusere på om søknadsskjemaets punkter om selve miljørisikovurderingen, del (section) 5 i søknadsskjemaet.

VKM viser til gjennomgangen av de enkelte punkter i skjemaet i svaret på spørsmål 1. VKM vurderer at informasjonen i del 2 av søknadsskjemaet helhetlig vil være relevant og dekkende for å kunne gi en begrunnet vurdering av miljørisiko. Del 5 er en spisset miljørisikoanalyse basert først og fremst på informasjonen som ble oppgitt i del 2, og noe fra del 3. Dersom søker har gitt utfyllende informasjon på alle punktene i delene 2 og 3 bør miljørisikovurderingen, del 5, kunne gjennomføres på en tilfredsstillende måte.

VKM konkluderer med at søknadskjemaet er i tråd med kravene til vurdering av helse og miljørisiko. VKM vil kunne foreta en helse- og miljørisikovurdering på bakgrunn av opplysninger som innhentes i skjemaet.
VKM vurderer det dithen at noe av informasjonen som oppgis om den kliniske studien i del 3 av skjemaet også er relevant for vurdering av miljørisiko. Spesielt bør man ha vurdert om hvordan håndtering av potensiell utskilling av virus-vektor i kroppsvæsker fra pasient som for eksempel oppkast, bleier etc. I denne sammenheng er informasjon om bruk av desinfeksjonsmidler og avfallshåndtering, (se kommentar del 4), tilpasset lokale eller nasjonale krav, relevant informasjon som søkeren bør kunne fremvise. Dette vil gjøre at

uheldig utskillelse og søl av virus-vektor kan håndteres på en slik måte at sikkerhet er ivaretatt.

2.3 Etter VKMs vurdering, er det andre aspekter ved søknadsskjemaet som bør tillegges vekt i vurderingen, som ikke dekkes av spørsmålene fra Miljødirektoratet?

Nei.