MINUTE Classification of self-amplifying mRNA influenza vaccine			
To	Raj Bhula Gene Technology Regulator	**Approved**	30 March 2022
	comments.		
Through	Heidi Mitchell Acting Assistant Secretary Evaluation Branch	Cleared	29 March 2022
	Legal Officer Legal Section	Cleared?	**Enter date**
	No legal advice is available on this minute		
	comments.		
	[redacted] Assistant Director Contained Dealings Evaluation Section	Cleared	24 March 2022
	comments.		
Action officer	[redacted] Evaluator, Contained Dealings Evaluation Section		23 March 2022
In relation to	Classification of self-amplifying mRNA influenza vaccine		
Files	E21-12230; D22-762881	**CCI files** (if applicable)	N/A
Purpose of this Minute	To seek your decision on whether self-amplifying mRNA vaccines delivered by nanoparticles should be considered a GMO.		

1. *Issue*

On 22 March 2022, the OGTR received a query from (D22-758243) from [redacted] who is the [redacted] contact for Seqirus Pty Ltd, a company involved in manufacturing vaccines, based in Melbourne. The query seeks advice from the OGTR on whether an influenza self-amplifying mRNA (sa-mRNA vaccine) is classified as a GMO under Australian law.

2. *Background*

There are wide interests in mRNA vaccine technology [redacted]

In contrast, self-amplifying mRNA (sa-mRNA) vaccines contains mRNA that encode both the antigen of interest and additional proteins that can amplify the antigen-encoding mRNA sequence (e.g. non-structural proteins; nsPs from alphaviruses). Both conventional and sa-mRNA vaccines have been used in preclinical studies against various diseases including influenza, respiratory syncytial virus, rabies, ebola and HIV-1 (Bloom, 2021). It is predicted that the sa-mRNA platform could lead to enhanced and prolonged antigen expression, which might lower dosage requirements and potentially result in less adverse reactions to the vaccine.

Seqirus is proposing to carry out a phase 1 first in human clinical trial using a monovalent sa-mRNA [redacted] influenza vaccine. The vaccine would consist of mRNA encoding the [redacted] and nsP 1-4 genes that encode for replicase genes from the Venezuelan equine encephalitis alphavirus (VEEV). The replicase genes enables self-amplification of the target genes on delivery into the cytoplasm of the host target cells via a lipid nanoparticle. The GM vaccine would not contain any VEEV structural protein genes (capsid or envelope), hence would not be able to form a new viral particle. The Seqirus IBC has assessed the product not to be a GMO because it is incapable of reproduction and incapable of transferring genetic material but requested further advice from OGTR. Their assessment has also considered the classification of these types of vaccines in other jurisdictions.

3. *Classification of previous clinical trial using sa-mRNA technology*

The GM vaccine proposed by Seqirus was produced using the same technology as one of the GM vaccines used in the prime/boost vaccination model in DNIR-606. The GM vaccine used in DNIR-606 consists of mRNA that encoded patient specific tumour-specific neoantigens (driven by internal sub genomic promoters), 2 universal class II MHC helper epitopes and nsP 1-4 genes from the VEEV. It also lacked any VEEV structural protein genes and [redacted]

[redacted] was previously consulted on the GM vaccine in DNIR-606 and provided [redacted] that it met the definition of a GMO because the viral vaccine meets the definition of an 'organism'. This is defined in Section 10 of the *Gene Technology Act 2000* as viable; capable of reproduction; or capable of transferring genetic material (D19-1298082). The [redacted] given was because the viral mRNA vaccine:

- can replicate; and
- may be considered to have an innate capacity to transfer its genetic material by recombination with a wild type alphavirus (although highly unlikely as alphaviruses only rarely

recombine and the parent virus, which would be the most likely to recombine, is not present in Australia) or by complementation by a helper virus (may be possible by related alphaviruses in Australia).

4. Recommendations

- Agree if you are satisfied, that, based on the available information, sa-mRNA vaccines using VEEV technology (with nsP1-4 genes and without any structural genes e.g. capsid and envelope) are defined as genetically modified organisms under the *Gene Technology Act 2000*.

Agree

- If agreed, a draft letter to the Seqirus representative is at (D22-762877). Your approval is sought for OGTR staff to send the e-mail on your behalf.

Agree

5. References

Bloom K, van den Berg F, Arbuthnot P. Self-amplifying RNA vaccines for infectious diseases. Gene Ther. 2021;28(3-4):117-29.

[redacted]

From: [redacted]
Sent: Tuesday, 5 November 2019 12:02 PM
To: [redacted]
Cc: [redacted] Dornbusch, Michael; [redacted]
Subject: FW: Agreement on GMO or not advice for DNIR 606 [SEC=OFFICIAL, ACCESS=Legal-Privilege]
Attachments: [redacted] correspondence about GRT-R902-GM or not GM 2019-10-23.DOCX; Nanoparticle RNA advice (FINAL).docx

Hi [redacted]
If I'm not mistaken, we had a very preliminary discussion about this with [redacted] some weeks ago.

I have read the attachments and [redacted] email below.

Based on the information provided, I agree with [redacted] that GRT-R902 is a GMO, and does require a DNIR approval. Please proceed and advise the Applicant accordingly.

Thanks,
Raj.

Dr Raj Bhula
Gene Technology Regulator
Office of the Gene Technology Regulator
Australian Government Department of Health
T: [redacted] | Free Call: 1800 181 030
E: Raj.Bhula@health.gov.au
Location: Level 11 Scarborough House, Atlantic Street, Woden, ACT 2606
Postal: MDP 54, GPO Box 9848, Canberra ACT 2601, Australia

Executive Assistant to the Gene Technology Regulator
[redacted]
T: [redacted] | E: [redacted]

The Department of Health acknowledges the Traditional Custodians of Australia and their continued connection to land, sea and community. We pay our respects to all Elders past and present.

From: [redacted]
Sent: Tuesday, 5 November 2019 11:12 AM
To: BHULA, Raj <Raj.Bhula@health.gov.au>
Cc: [redacted] Dornbusch, Michael <Michael.Dornbusch@health.gov.au>; [redacted]
Subject: Agreement on GMO or not advice for DNIR 606 [SEC=OFFICIAL, ACCESS=Legal-Privilege]

Dear Raj,
Please find below some advice from [redacted] on whether a GMO currently under assessment as part of DNIR 606 meets the definition of a GMO in the *Gene Technology Act 2000*. [redacted] has given advice that it **does** fall under the Act. Please could you confirm that you agree with this advice that GRT-R902 is a GMO under the Act and we will proceed with the DNIR assessment on that basis and the planned consultation with GTTAC.

We are available to discuss any aspects of this

Kind regards

[redacted]

[redacted]
Director
Contained Dealings Evaluation Section

Office of the Gene Technology Regulator
Australian Government Department of Health
T: [redacted] | Free call: 1800 181 030
E: [redacted] Web: www.ogtr.gov.au
Location: 11th floor, Scarborough House, Atlantic Street, Woden Town Centre, ACT 2606
Postal: MDP-54, GPO Box 9848, Canberra ACT 2601, Australia

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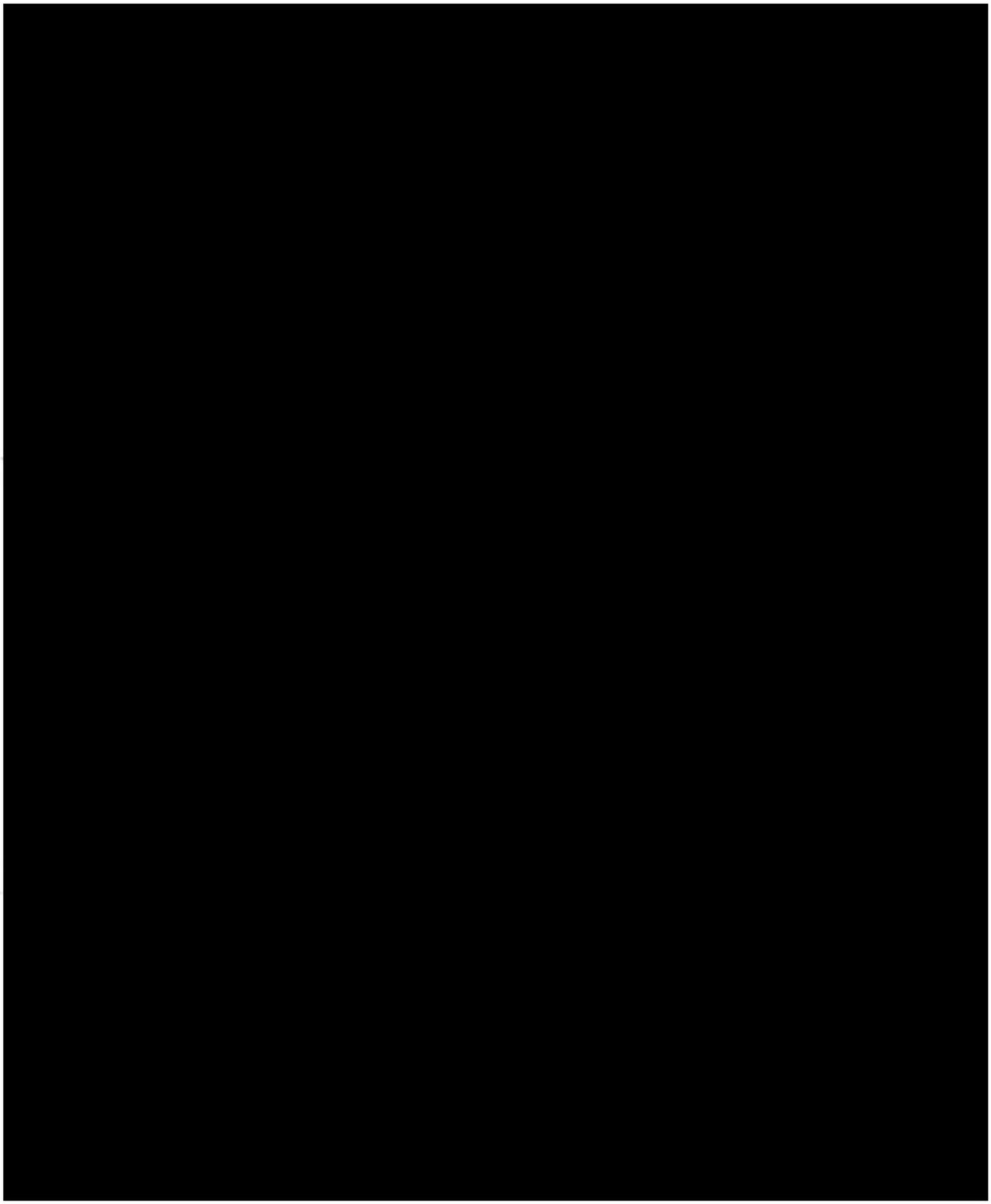
From: [redacted]
Date: Wednesday, 23 Oct 2019, 6:09 pm
To: [redacted]
Cc: [redacted]
Subject: RE: GMO1/GMO2 comparison [SEC=OFFICIAL, ACCESS=Legal-Privilege]

This email may contain CCI

Legal Advice in Confidence

[redacted]



From: [redacted]
Sent: Wednesday, 23 October 2019 9:09 AM
To: [redacted]
Cc: [redacted]
Subject: GMO1/GMO2 comparison [SEC=OFFICIAL]

Good morning [redacted]

Please find attached a document highlighting the differences and similarities between the mRNA encapsulated in a lipid nanoparticle we discussed and the GM viral vector from DNIR-606. I have also highlighted the differences between the mRNA you provided advice for in 2016 and the mRNA used in DNIR-606.

Please let me know you need additional information
Cheers
[redacted]
Evaluator

Office of the Gene Technology Regulator
Australian Government Department of Health
T: [redacted] | E: [redacted]

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[redacted]

[redacted]

In the case of GMO2, the mRNA encapsulated in the nanoparticle is from viral origin and was rendered replication deficient by deletion of structural genes. This viral mRNA may be considered to have an innate capacity to transfer their genetic material by recombination with a wild type alphavirus (although highly unlikely as alphaviruses only rarely recombine and the parent virus, which would be the most likely to recombine, is not present in Australia) or by complementation by a helper virus (may be possible by related alphaviruses in Australia). In this instance, this GMO is very similar to an adenovirus, which we routinely assess as a DNIR.

	GMO1 (GRT-C901)	GMO2 (GRT-R902)
Parent organism	Chimpanzee adenovirus	Venezuelan equine encephalitis virus
Deletion of viral genes	**E1 gene deletion**: [redacted] **E3 gene deletion**: renders the virus more vulnerable to the immune system	**Deletion of the structural genes**; [redacted] The remaining mRNA is a self-amplifying mRNA (SAM) which includes the replication machinery of the Venezuelan Equine Encephalitis.
Packaging	Viral particles are produced by co-cultivating the GMO with cell line HEK 293 providing the deleted E1. The viral particles produced can only infect cells once.	To deliver the SAM to the targeted human cells, it has been formulated with lipid nanoparticles (LNPs) composed of [redacted] lipids:. These lipids can be individually sourced from various companies but the applicant did not provide any information about the origin of these lipids.
Infection	The adenovirus enter the cells by binding to CAR proteins present on the host/patient cells. Once internalized, the virus is uncoated and the viral genome is transported to the nucleus. Viral protein are expressed but the virus does not replicate and remains confined to the infected cell.	This GMO enters the host/patient cells by phagocytosis. Both the lipid nanoparticle and the cell lipid membrane fuse and the lipid nanoparticle is internalised into the cell. The mRNA is released in the cytoplasm and starts replicating, producing more RNA (both coding strand and non-coding strand), which will then be translated into proteins. The viral mRNA remains confined to the infected cell.
Genome integration	The viral DNA is not integrated into the patient genome.	The viral RNA is not integrated into the patient genome.

[redacted]

From: [redacted]
Sent: Thursday, 11 June 2020 11:22 AM
To: [redacted]
Cc: [redacted]
Subject: FW: Agreement on GMO or not advice for DNIR 606 [SEC=OFFICIAL, ACCESS=Legal-Privilege]
Attachments: [redacted]correspondence about GRT-R902-GM or not GM 2019-10-23.DOCX; Nanoparticle RNA advice (FINAL).docx

Hi [redacted]

This is some info about whether an encapsulated mRNA was a GMO or not. There is a comparison with a replication-defective adenovirus, which OGTR regulates. Although below you are questioning whether this RD virus should in fact be regulated, there is some useful info in these documents that supports this.

Cheers
[redacted]

From: [redacted]
Sent: Thursday, 11 June 2020 10:29 AM
To: [redacted]
Subject: FW: Agreement on GMO or not advice for DNIR 606 [SEC=OFFICIAL, ACCESS=Legal-Privilege]

Hi [redacted]

This e mail contains a comparison document I have written to justify the GM classification of the product. The second document is the advice written by [redacted]

Cheers
[redacted]

From: BHULA, Raj <Raj.Bhula@health.gov.au>
Sent: Tuesday, 5 November 2019 12:02 PM
To: [redacted]
Cc: [redacted] Dornbusch, Michael <Michael.Dornbusch@health.gov.au>; [redacted]
Subject: FW: Agreement on GMO or not advice for DNIR 606 [SEC=OFFICIAL, ACCESS=Legal-Privilege]

Hi [redacted]
If I'm not mistaken, we had a very preliminary discussion about this with [redacted] some weeks ago.

I have read the attachments and [redacted] email below.

Based on the information provided, I agree with [redacted] that GRT-R902 is a GMO, and does require a DNIR approval. Please proceed and advise the Applicant accordingly.

Thanks,
Raj.

Dr Raj Bhula
Gene Technology Regulator

Office of the Gene Technology Regulator
Australian Government Department of Health
[redacted] | Free Call: 1800 181 030
E: [redacted]
Location: Level 11 Scarborough House, Atlantic Street, Woden, ACT 2606
Postal: MDP 54, GPO Box 9848, Canberra ACT 2601, Australia

Executive Assistant to the Gene Technology Regulator
[redacted]
T: [redacted] E: [redacted]

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From: [redacted]
Sent: Tuesday, 5 November 2019 11:12 AM
To: BHULA, Raj <Raj.Bhula@health.gov.au>
Cc: [redacted] Dornbusch, Michael <Michael.Dornbusch@health.gov.au>; [redacted]
Subject: Agreement on GMO or not advice for DNIR 606 [SEC=OFFICIAL, ACCESS=Legal-Privilege]

Dear Raj,
Please find below some advice from [redacted] on whether a GMO currently under assessment as part of DNIR 606 meets the definition of a GMO in the *Gene Technology Act 2000*. [redacted] has given advice that it **does** fall under the Act. Please could you confirm that you agree with this advice that GRT-R902 is a GMO under the Act and we will proceed with the DNIR assessment on that basis and the planned consultation with GTTAC.

We are available to discuss any aspects of this

Kind regards
[redacted]

[redacted]
Director
Contained Dealings Evaluation Section

Office of the Gene Technology Regulator
Australian Government Department of Health
T: [redacted] Free call: 1800 181 030
E: [redacted] Web: www.ogtr.gov.au
Location: 11th floor, Scarborough House, Atlantic Street, Woden Town Centre, ACT 2606
Postal: MDP-54, GPO Box 9848, Canberra ACT 2601, Australia

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From: [redacted]
Date: Wednesday, 23 Oct 2019, 6:09 pm
To: [redacted]
Cc: [redacted]
Subject: RE: GMO1/GMO2 comparison [SEC=OFFICIAL, ACCESS=Legal-Privilege]

[redacted]

From: [redacted]
Sent: Wednesday, 23 October 2019 9:09 AM
To: [redacted]
Cc: [redacted]
Subject: GMO1/GMO2 comparison [SEC=OFFICIAL]

Good morning [redacted]

Please find attached a document highlighting the differences and similarities between the mRNA encapsulated in a lipid nanoparticle we discussed and the GM viral vector from DNIR-606. I have also highlighted the differences between the mRNA you provided advice for in 2016 and the mRNA used in DNIR-606.

Please let me know you need additional information
Cheers
[redacted]
Evaluator

Office of the Gene Technology Regulator
Australian Government Department of Health
T: [redacted] | E: [redacted]

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[redacted]

From: OGTR CDES
Sent: Monday, 31 October 2022 9:06 AM
To: [redacted]
Subject: RE: mRNA vaccines [SEC=OFFICIAL]

Dear [redacted]

Thank you for contacting the OGTR with you query regarding mRNA vaccines.

Some RNA vaccines are excluded from regulation under *the Gene Technology* Act 2000 (the Act) while others are not. Vaccines based on mRNA that are incapable of giving rise to infectious agents or reproduction are excluded from regulation under the Act, and do not require any assessment by the OGTR. This is the case for example of the two mRNA covid-19 vaccines currently available in Australia.

However, self-amplifying RNA (saRNA) vaccines are considered genetically modified organisms (GMOs), on the basis that the nucleic acid is capable of reproduction. The clinical trial of a saRNA vaccine is a licensable dealing.

Please do not hesitate to contact us if you have further questions.

Kind regards
[redacted]

[redacted]
Evaluator – Contained Dealings Evaluation Section
Office of the Gene Technology Regulator | Evaluation Branch
Australian Government, Department of Health and Aged Care
T: [redacted] | E: [redacted]
Location: Scarborough House, Level 11, Woden, ACT 2606
GPO Box 9848, Canberra ACT 2601, Australia

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From: [redacted]
Sent: Friday, 28 October 2022 8:48 AM
To: OGTR CDES <OGTR.CDES@health.gov.au>
Subject: mRNA vaccines

Good morning,

I haven't had a lot of licencable work come through in the last year but wanted to ask a question to make sure I'm giving the right advice.

In my sphere I'm seeing many mRNA vaccines coming in from China for first in human clinical trials. As these are not biologicals (by the TGA's definition), they are not being evaluated by a regulatory authority for safety and going in through the CTN system – which is one of the great attractions of coming to Australia for these trials.

In any case, these therapies as products do not fall under the remit of the Gene Technology Act / Regulations as licencable dealings. My question is whether the OGTR are interested in any kind of involvement in the assessment of these mRNA vaccines and similar products.

Looking forward to your response.

Kind regards,

[redacted]

BioPharma Regulatory Consulting
www.biopharmarc.com.au

BPR
BioPharma Regulatory Consulting

[redacted]

From: [redacted]
Sent: Monday, 7 August 2023 11:36 AM
To: [redacted]
Subject: RE: mRNA vaccine [SEC=OFFICIAL]
Attachments: Examples of mRNA dealings and classification.pptx

Dear [redacted]

Thank you for your patience.

Please find below some generic information regarding the manufacture and administration of mRNA vaccines. I have also attached a document with few examples of how these dealings may be classified.

Manufacture of mRNA vaccines

- The mRNA only encodes antigen(s) which are unable to give rise to an infectious agent
  - **The manufacturing of the mRNA vaccine involves the production of less than 25 L of GMO culture in each vessel**- Some of the steps in the manufacturing process would be classified as an exempt dealing.
  - **The manufacturing of the mRNA vaccine involves the production of more than 25 L of GMO culture in each vessel and the GMO is produced in a PC2 Large Scale facility-** This would be classified as a Notifiable Low Risk Dealing (NLRD).
- The mRNA is a self-amplifying mRNA (samRNA)
  - **The manufacturing of the samRNA vaccine involves the production of less than 25 L of GMO culture in each vessel**- The initial step of the production (pDNA production) would likely be classified as an exempt dealing, and the subsequent steps would be classified as an NLRD.
  - **The manufacturing of the samRNA vaccine involves the production of more than 25 L of GMO culture in each vessel** - this would be classified as a licence whether or not the manufacturing facility is OGTR certified.

Administration of mRNA vaccine into animal

Following administration of either mRNA or samRNA vaccines into animals, it is expected the lipid nanoparticle (LNP) would facilitate entry of the mRNA into the animal cells, and as a result, these cells would become genetically modified. For a short amount of time, until an immune response is triggered and those cells are destroyed by the host immune response, these animals would be considered GMOs. These dealings would be classified as a NLRD if the administration occurs in an OGTR certified facility.

If, however, the administration and keeping of animals are to occur outside of containment, that is not in an OGTR certified indoor or large grazing animal outdoor facility, you would require a DIR licence.

Please do not hesitate to contact us if you have any questions or require further clarification.

This response is general information and does not constitute a legal advice.

Kind regards,

[redacted]
Evaluator – Contained Dealings Evaluation Section
Office of the Gene Technology Regulator | Evaluation Branch
Australian Government, Department of Health and Aged Care
T: [redacted] | E: [redacted]

Location: Scarborough House, Level 11, Woden, ACT 2606
GPO Box 9848, Canberra ACT 2601, Australia

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From: [redacted]
Sent: Thursday, 6 July 2023 12:46 PM
To: [redacted]
Subject: Re: mRNA vaccine [SEC=OFFICIAL]

Hi [redacted]

Thank you for the quick response.

I am [redacted] and neither the committee nor I have experience in mRNA vaccines yet. I am looking into commercial suppliers to produce a lipid nanoparticle self-amplifying mRNA vaccine and I expect other people in Tasmania will be in the coming year given their success in humans.

The initial uses would be encoding neoantigens and genes to upregulate expression of antigen processing and presentation in rats and mice in PC2 facilities.

Kind regards
[redacted]

--
[redacted]
Menzies Institute for Medical Research
University of Tasmania
Private Bag 23, Hobart TAS 7000
t: [redacted] | m: [redacted] | e: [redacted]
@WildImmunity | WildImmunity.com
Wild and Comparative Immunology Consortium

From: [redacted]
Sent: Wednesday, July 5, 2023 6:13:02 PM
To: [redacted]
Subject: RE: mRNA vaccine [SEC=OFFICIAL]

Dear [redacted]

Thank you for your email.

Manufacturing of mRNA vaccine and their use may be regulated under the *Gene Technology Act 2000* (the Act). This will depend on whether gene technology was used in the manufacturing process and whether the final product, mRNA vaccine, meets the definition of an organism, as defined in the Act (see below).

organism means any biological entity that is:

(a) viable; or
(b) capable of reproduction; or
(c) capable of transferring genetic material.

For example, lipid nanoparticle self-amplifying mRNA vaccines are classified as GMOs, as they are capable of reproduction and transferring genetic material.

I suggest contacting your Institutional Biosafety Committees (IBC) for the classification of the proposed dealings. If you would like a more tailored advice from us, please provide information on the manufacturing process, the mRNA vaccine and the transgenes proposed to be inserted in the vaccine.

Kind regards,

[redacted]

[redacted]
Evaluator – Contained Dealings Evaluation Section
Office of the Gene Technology Regulator | Evaluation Branch
Australian Government, Department of Health and Aged Care
T: [redacted] | E: [redacted]
Location: Scarborough House, Level 11, Woden, ACT 2606
GPO Box 9848, Canberra ACT 2601, Australia

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From: [redacted]
Sent: Tuesday, 4 July 2023 9:41 AM
To: [redacted]
Subject: mRNA vaccine

REMINDER: Think before you click! This email originated from outside our organisation. Only click links or open attachments if you recognise the sender and know the content is safe.

Dear [redacted]

My team will likely be testing mRNA vaccines for some related projects in the near future. As the technology is fairly new, I am not sure where it fits in the Regulations.

Can you steer me towards the correct type of dealing for in vitro testing of mRNA vaccines and trials in non-genetically modified laboratory mice and rats.

Kind regards,

[redacted]

--

[redacted]

[redacted]

[redacted]

Menzies Institute for Medical Research

University of Tasmania

t: [redacted] | e: [redacted]

Website: WildImmunity.com | Facebook: WildImmunity

Twitter: @WildImmunity | Youtube: @WildImmunity

Wild and Comparative Immunology Consortium

Recent publication: Class II transactivator induces expression of MHC-I and MHC-II in transmissible Tasmanian devil facial tumours (*Open Biology*)

Recent publication: A human adenovirus encoding IFN-? can transduce Tasmanian devil facial tumour cells and upregulate MHC-I (*Journal of General Virology*)

Recent publication: Fluorescent Adaptable Simple Theranostic (FAST) proteins for single-step testing of recombinant proteins (*Science Advances*)

menzies.utas.edu.au

UNIVERSITY of TASMANIA

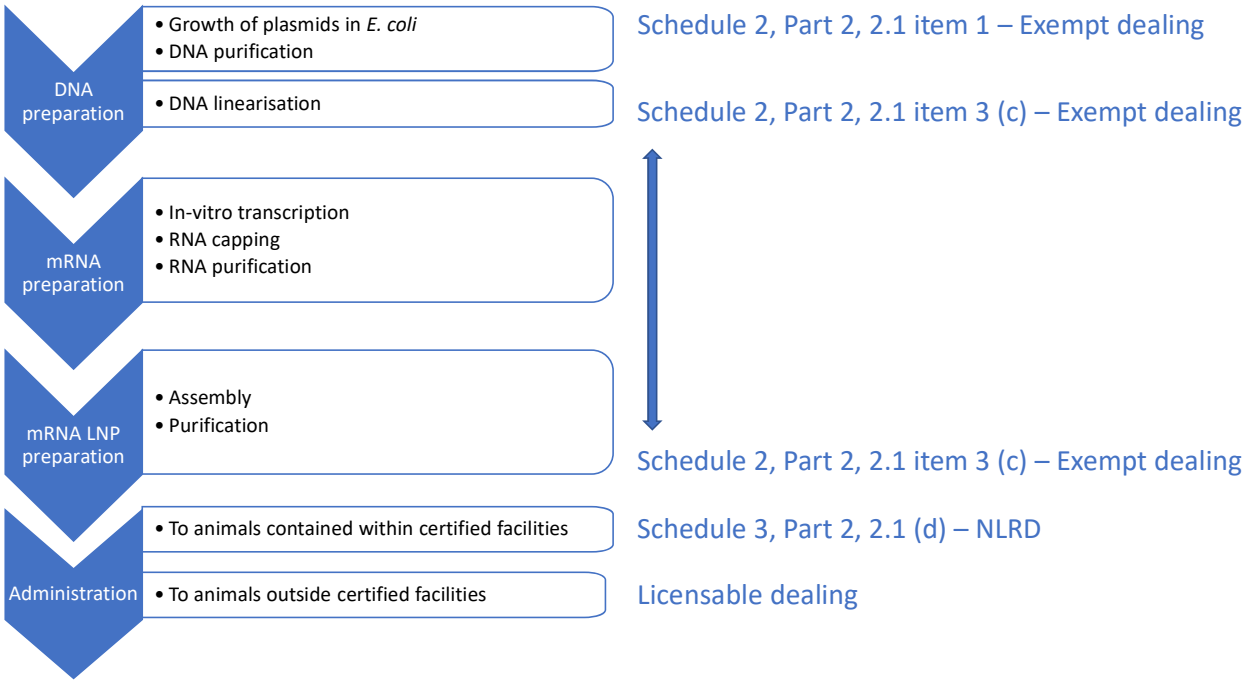
MENZIES

Institute for Medical Research

CRICOS 00586B

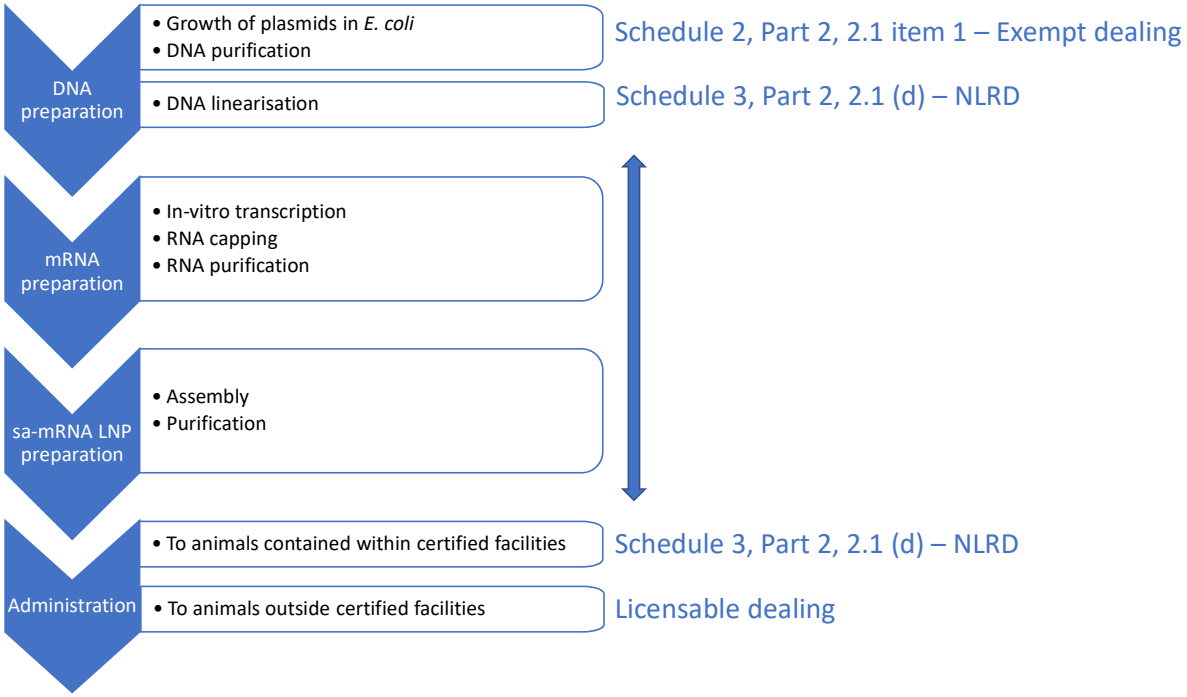
Manufacturing and administration of mRNA vaccines (that are not self-amplifying)

- under 25 L of GMO culture in a single vessel;
- donor nucleic acid meets the requirements in Schedule 2, Part 1, Item 4 (2).



Manufacturing and administration of self-amplifying mRNA vaccines

- under 25 L of GMO culture in a single vessel;



Manufacturing of mRNA vaccines – over 25 L in a single vessel

• dealing is undertaken within a PC2 large Scale certified facility; • donor nucleic acid meets the requirements in Schedule 2, Part 1, Item 4 (2)	Schedule 3, Part 2, 2.1 (f) – NLRD
• dealing is undertaken outside a certified facility.	Licensable dealing

Manufacturing of self-amplifying mRNA vaccines – over 25 L in a single vessel

• dealing is undertaken within or outside a certified facility.	Licensable dealing

[redacted]

From: OGTR CDES <OGTR.CDES@health.gov.au>
Sent: Friday, 3 February 2023 2:25 PM
To: [redacted]
Subject: RE: Enquiry on behalf of Vertex Australia re Clinical Trials for a Gene Therapy Product [SEC=OFFICIAL]

Dear [redacted]

Thank you for your query regarding the classification of a clinical trial using an mRNA gene therapy product for the treatment of Cystic Fibrosis.

Some RNA vaccines/gene therapies are excluded from regulation under *the Gene Technology* Act 2000 (the Act) while others are not. Vaccines/gene therapies based on mRNA that are incapable of giving rise to infectious agents or reproduction are excluded from regulation under the Act, and do not require any assessment by the OGTR.

However, please be aware that self-amplifying RNA (saRNA) vaccines/gene therapies are considered genetically modified organisms (GMOs), on the basis that the nucleic acid is capable of reproduction. The clinical trial of a saRNA vaccine/gene therapy is a licensable dealing.

Please also be aware that your organisation may need authorisation under the Act if manufacture of the GMO is to take place in Australia. This authorisation is likely to be a notifiable low risk dealing (NLRD) and is likely to be assessed by an institutional biosafety committee rather than the OGTR.

Please do not hesitate to contact us if you have further questions.

Kind regards,

[redacted]

Evaluator

Office of the Gene Technology Regulator | Evaluation Branch
Australian Government, Department of Health and Aged Care
T: [redacted] E: [redacted]
Location: Scarborough House, Level 11, Atlantic Street,
Woden Town Centre, ACT 2606
PO Box 9848, Canberra ACT 2601, Australia

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From: [redacted]
Sent: Friday, 3 February 2023 11:34 AM
To: OGTR CDES <OGTR.CDES@health.gov.au>
Subject: Enquiry on behalf of Vertex Australia re Clinical Trials for a Gene Therapy Product

Dear Office of the Gene Technology Regulator,

I wanted to reach out to you on behalf of Vertex Pharmaceuticals Australia to enquire about conducting human clinical trials for gene therapy product, known as VX-522, to be trialled for the treatment of Cystic Fibrosis

Brief Product description:
VX-522 consists of a chemically modified mRNA (VX-522 mRNA) that encodes normal, functional CFTR protein formulated into lipid nano particles and intended for delivery to cystic fibrosis lung epithelial cells via oral inhalation using a nebulizer

- ➔ We would like to enquire what type of licence (if any) we require to initiate trials in Australia for this product? and whether Vertex would need to be 'accredited' prior to submitting an application for the licence?

If any further information relating to the product is required to make this determination, please let me know

Thank you in advance for your guidance,

Kind regards,

[redacted]

[redacted]

Vertex Pharmaceuticals
Suite 3 Level 3
601 Pacific Highway
St Leonards NSW 2065
AUSTRALIA
Mobile: [redacted]
Email: [redacted]
www.vrtx.com

We acknowledge the Cammeraygal people of the Eora Nation, the Traditional Custodians of the land on which we gather. We also acknowledge Traditional Owners of Country throughout Australia and to their continuing connection to land, sea and community. We pay respects to them and to their Elders past and present.

[redacted]

From: OGTR CDES
Sent: Friday, 17 March 2023 2:53 PM
To: [redacted]
Cc:
Subject: RE: Opinion on DNIR License Need for an mRNA Investigational Product [SEC=OFFICIAL]

Dear [redacted]

Thank you for contacting the OGTR with your query.

Some RNA vaccines are excluded from regulation under *the Gene Technology* Act 2000 (the Act) while others are not. If the mRNA does not meet the definition of an 'organism' as defined in the Act, they are excluded from regulation under the Act, and do not require any assessment by the OGTR. For example, the two mRNA COVID-19 vaccines currently available in Australia. If the mRNA meets the definition of an 'organism' as defined in the Act, they are considered genetically modified organisms (GMOs). The self-amplifying or self-replicating RNA encapsulated in lipid nanoparticles meets the definition of an 'organism' on the basis that the nucleic acid is capable of reproduction and transferring genetic material. Therefore, a clinical trial with a self-amplifying or self-replicating RNA would require an authorisation from the OGTR.

Section 10 of the Act defines an organism as viable; capable of reproduction; or capable in transferring genetic material. The definition of an organism in the Act takes into account the capability of this organism to reproduce or transfer its genetic material rather than the likelihood of these occurring.

We have reviewed the information provided in your email. The investigational product (STX-001), a self-replicating mRNA encoding IL-12 encapsulated in lipid nanoparticle, is considered a GMO and the introduction of this GMO into a person will require a DNIR licence.

Additional information:

Human clinical trials involving genetically modified organisms (GMOs) either require a licence (DNIR or DIR) or in certain cases (GM human somatic cells that meet the additional criteria specified in Schedule 3 Part 3 (n) of the Gene Technology Regulations 2001) may be exempt dealings. The category of licence depends on whether or not the GMO is expected to be shed or excreted from trial participants or transmitted by trial participants (i.e., is the GMO likely to be contained in the body of trial participants; or are viable GMOs likely to be shed in body fluids or excreta of trial participants, or transmissible by insects likely to come into contact with trial participants, and thereby released into the environment). If the GMO is not likely to be shed or excreted or transmitted, a Dealing Not involving Intentional Release (DNIR) licence is required. If the viable GMO has the potential to be shed, excreted or transmitted from trial participants, a Dealing Involving Intentional Release (DIR) licence is required. Some further relevant information regarding clinical trials is provided on the OGTR website at Guidance for conducting human clinical trials involving GMOs | Office of the Gene Technology Regulator (ogtr.gov.au) which may be of assistance if you haven't already seen it.

The time frames for a decision on the licence application for:

- DNIR – 90 working days
- DIR (limited and controlled) – 150 working days (or 170 working days if a significant risk is identified)
- DIR (general/commercial) – 255 working days.

More information on the approval process and forms can be found at https://www.ogtr.gov.au/apply-gmo-approval.

- Overview of the approval process - https://www.ogtr.gov.au/apply-gmo-approval/overview-approval-process

- **Clinical trial form** – Apply for a licence to conduct a human clinical trial of a GMO | Office of the Gene Technology Regulator (ogtr.gov.au)

Please don't hesitate to contact us if you require further information.

Kind regards,

[redacted]

Assistant Director – Contained Dealings Evaluation Section

Office of the Gene Technology Regulator | Evaluation Branch
Australian Government, Department of Health and Aged Care
T: [redacted] | E: [redacted]
Location: Scarborough House, Level 11, Woden, ACT 2606
PO Box 9848, Canberra ACT 2601, Australia

The Department of Health and Aged Care acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.

From: [redacted]
Sent: Thursday, 16 March 2023 8:14 AM
To: VOICEMAIL, OGTR <OGTR.Voicemail@health.gov.au>
Cc: [redacted]
Subject: Opinion on DNIR License Need for an mRNA Investigational Product

Hi,

I am seeking the agency's opinion on whether obtaining a DNIR license for an investigational product (STX-001) is necessary.

STX-001 is a lipid nanoparticle (LNP)-encapsulated self-replicating mRNA encoding for the therapeutic payload interleukin-12 (IL-12; see Figure). It is intended to be injected directly into tumors to produce IL-12 locally and reduce tumor volume in patients with advanced solid tumors.

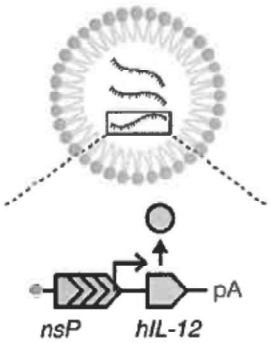


Figure: STX-001 is an LNP-encapsulated self-replicating mRNA encoding for the therapeutic payload IL-12 (nsP: non-structural polyprotein).

The mRNA is generated by in-vitro transcription from a plasmid encoding: an RNA-dependent RNA polymerase responsible for the mRNA self-replication process, the codon-optimized IL-12 coding sequence, and a poly(A) tail. The sequence of the RNA-dependent RNA polymerase (non-structural polyprotein) is derived from the Venezuelan-equine encephalitis virus (VEEV, an alphavirus). However, since no viral capsid protein sequences are encoded, there is no risk of virion production during manufacturing or in patients.

Please advise if a DNIR license should be sought before pursuing clinical trials in Australia.

Best

[redacted]

[redacted]

From: [redacted]
Sent: Friday, 21 April 2023 9:33 AM
To: [redacted]
Cc: [redacted]
Subject: RE: DNIR-606 - Clarification of CCI Application [SEC=OFFICIAL]

Dear [redacted]

During the assessment of the application (DNIR-606), the Regulator was consulted and made a decision that GRT-C902 meets the criteria of the definition for a GMO. Hence, DNIR-606 would still be required for the administration of the IP (GRT-C902).

[redacted]

Kind regards,

[redacted]

From: [redacted]
Sent: Thursday, 20 April 2023 4:12 PM
To: [redacted]
Cc: [redacted]
Subject: RE: DNIR-606 - Clarification of CCI Application [SEC=OFFICIAL]

'Hi [redacted]

This is a timely reminder as there are some developments with DNIR 606 for which we were about to submit the following query to the CDES regarding the preferred way forward for DNIR 606.

Regards,

[redacted]

'To whom it may concern,

The Peter MacCallum Cancer Centre (PMCC) is the holder of DNIR Licence 606: Clinical Study GO-004: An International Phase 1/2 Study of GRT-C901/GRT-R902, a Neoantigen Cancer Vaccine, in Combination with Immune Checkpoint Blockade for Patients with Advanced Solid Tumors.

The investigational product is a prime /boost vaccine which comprises:

- *GRT-C901- a vaccine which utilizes a chimpanzee adenovirus as the primary vaccination and*
- *GRT-C902- a self-amplifying mRNA (SAM) formulated in a lipid nanoparticle (LNP) that will be used for recurrent boost (up to 8) vaccinations following the GRT-C901 prime.*

The Trial principal investigator at PMCC, has notified the Peter Mac IBC that the final patient has received the initial primary vaccination and the first boost with the mRNA nanoparticles. The patient is then scheduled to just receive the boost vaccinations with GRT-C902.

We would like to seek the advice of the OGTR as to the options for the use of the GRT-C902 IP on its own for this final patient ONLY. The understanding of the IBC is that this boost component of the vaccine, mRNA encapsulated in liquid nanoparticles, is exempt from the requirement for a Licence and therefore would it be appropriate to remove GRT-C902 from the Licence?

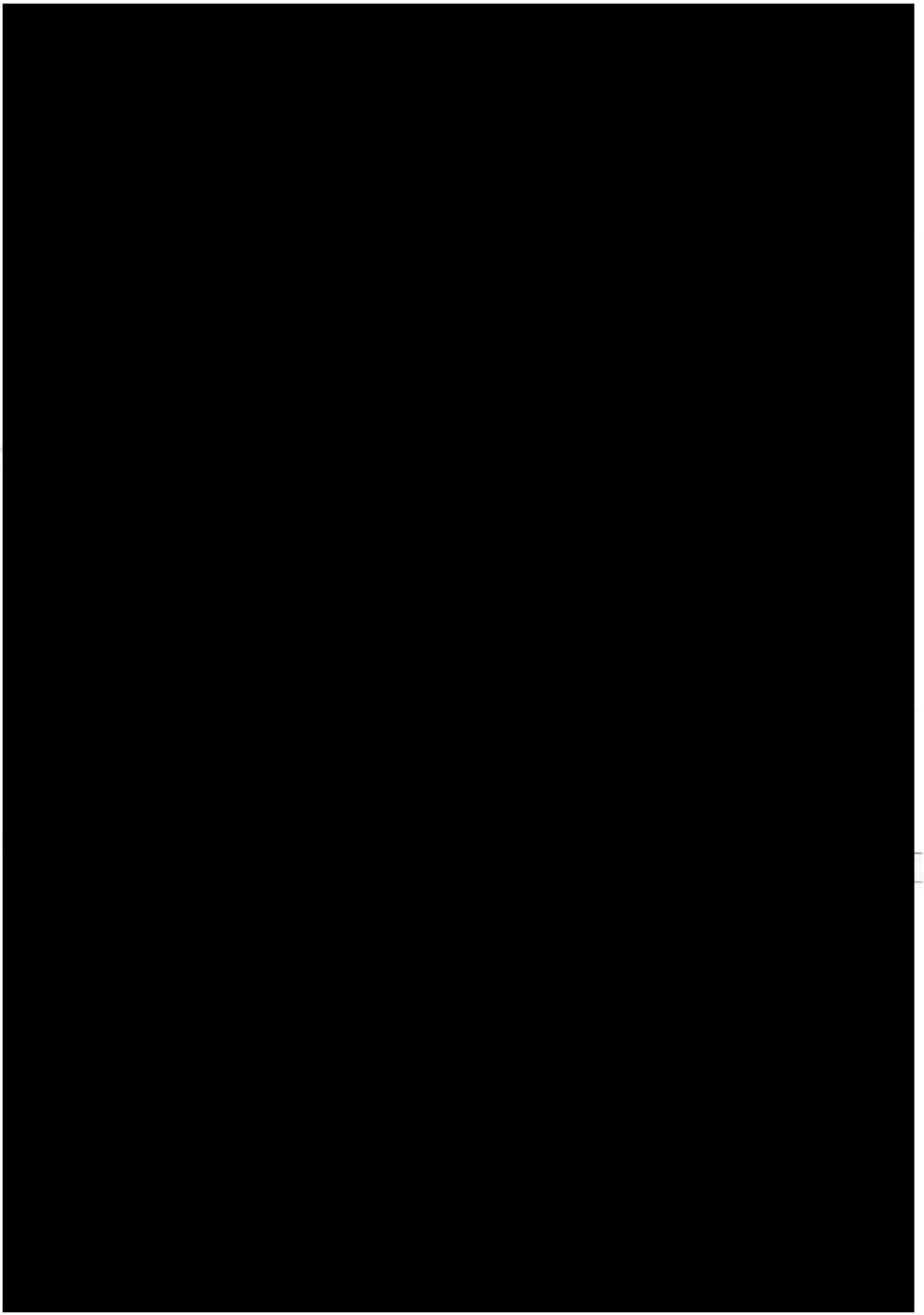
OR as this is the last patient to be treated do we request the termination of the Licence, effective ASAP? Again the understanding of the IBC is that the patient could continue to receive the boost vaccinations.

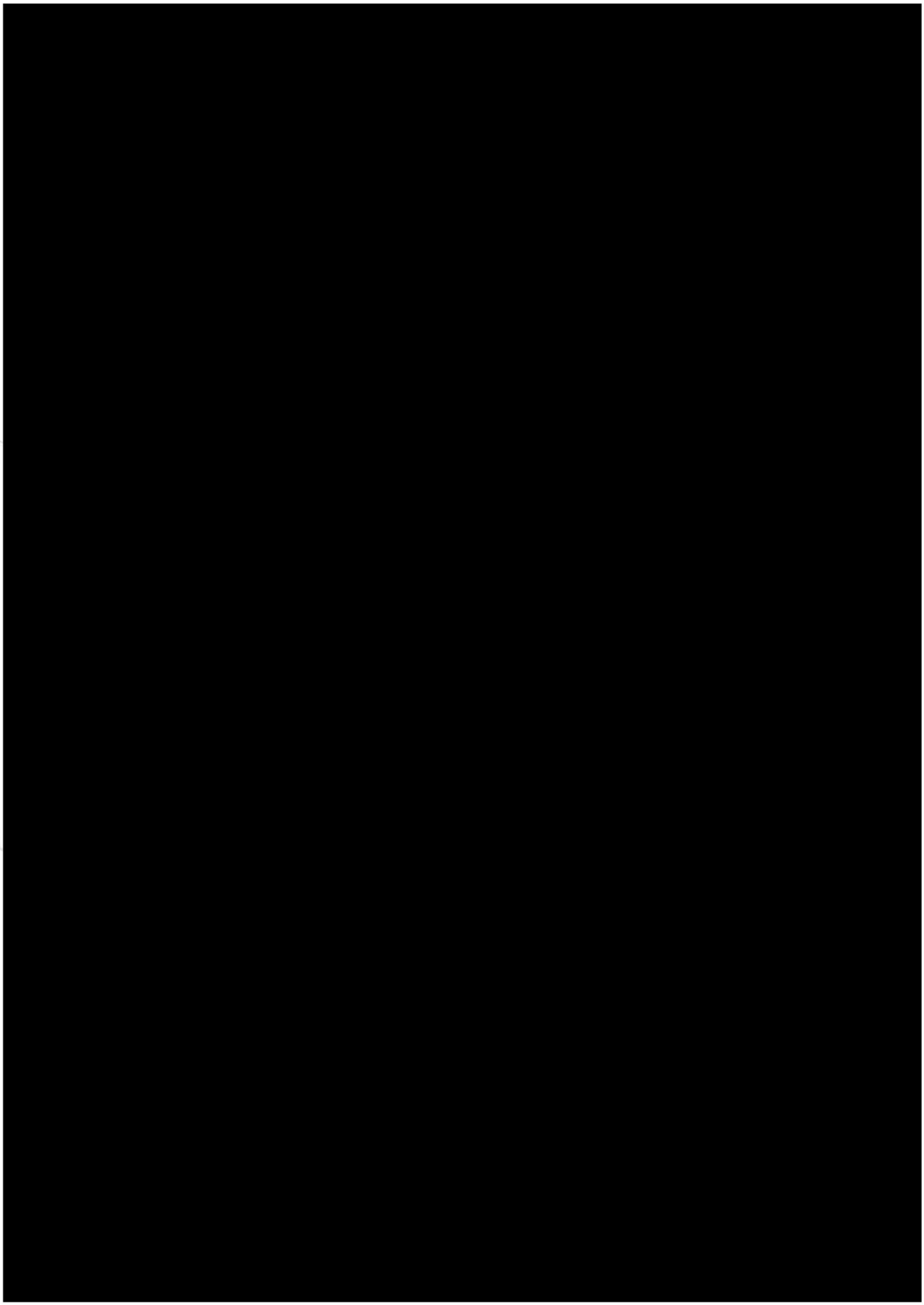
We would appreciate your advice on what action we should/can take.

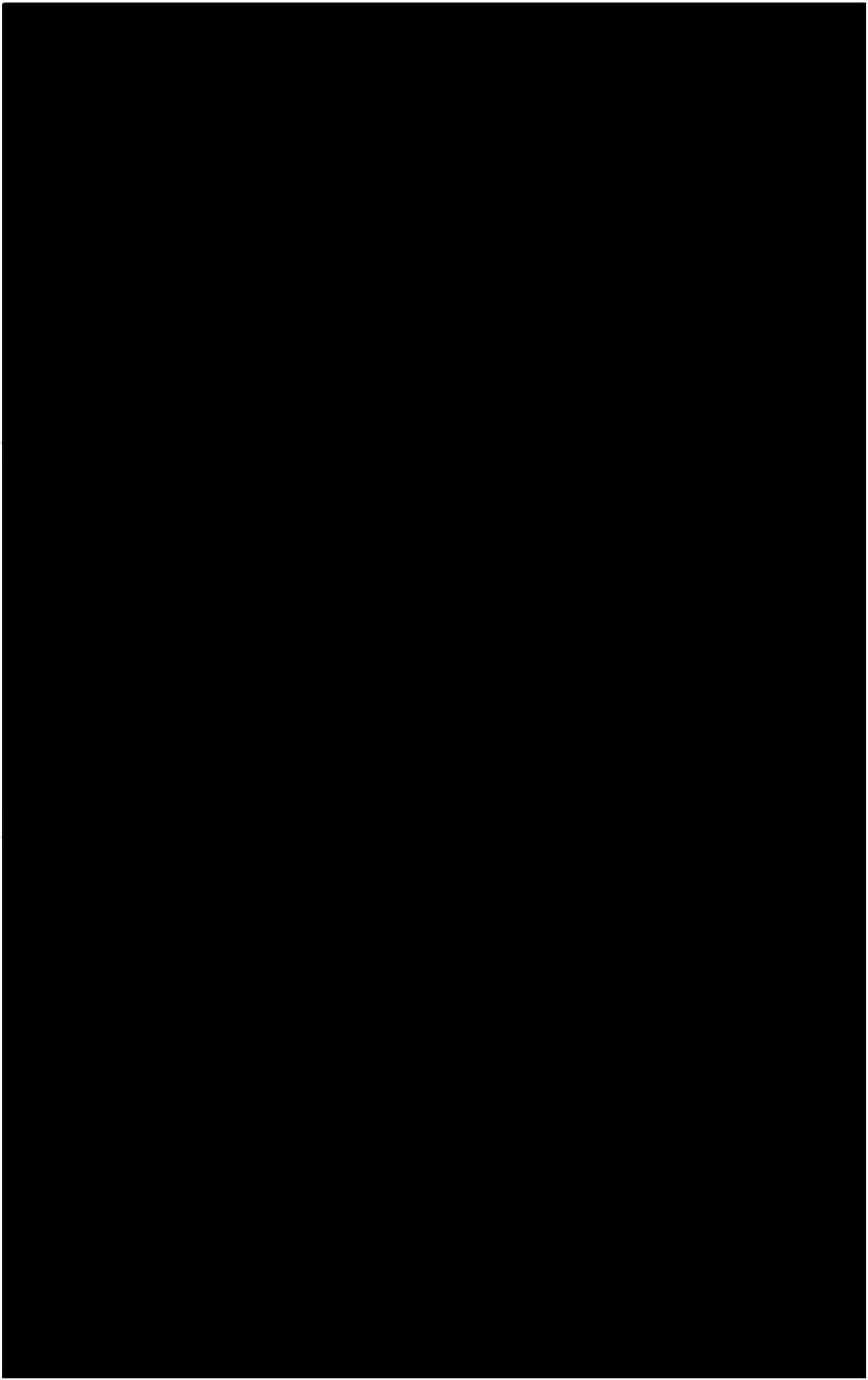
Kind regards

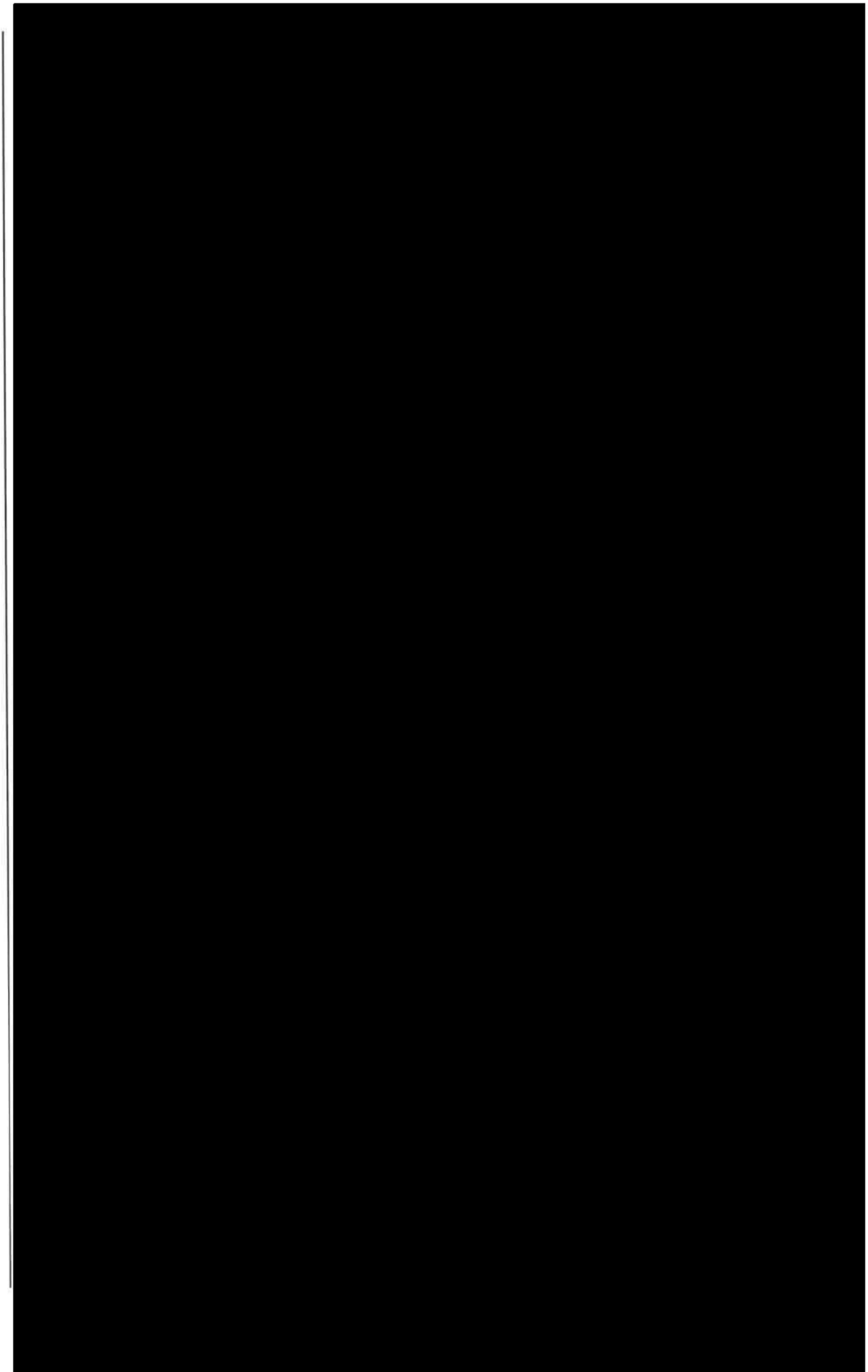
[redacted]

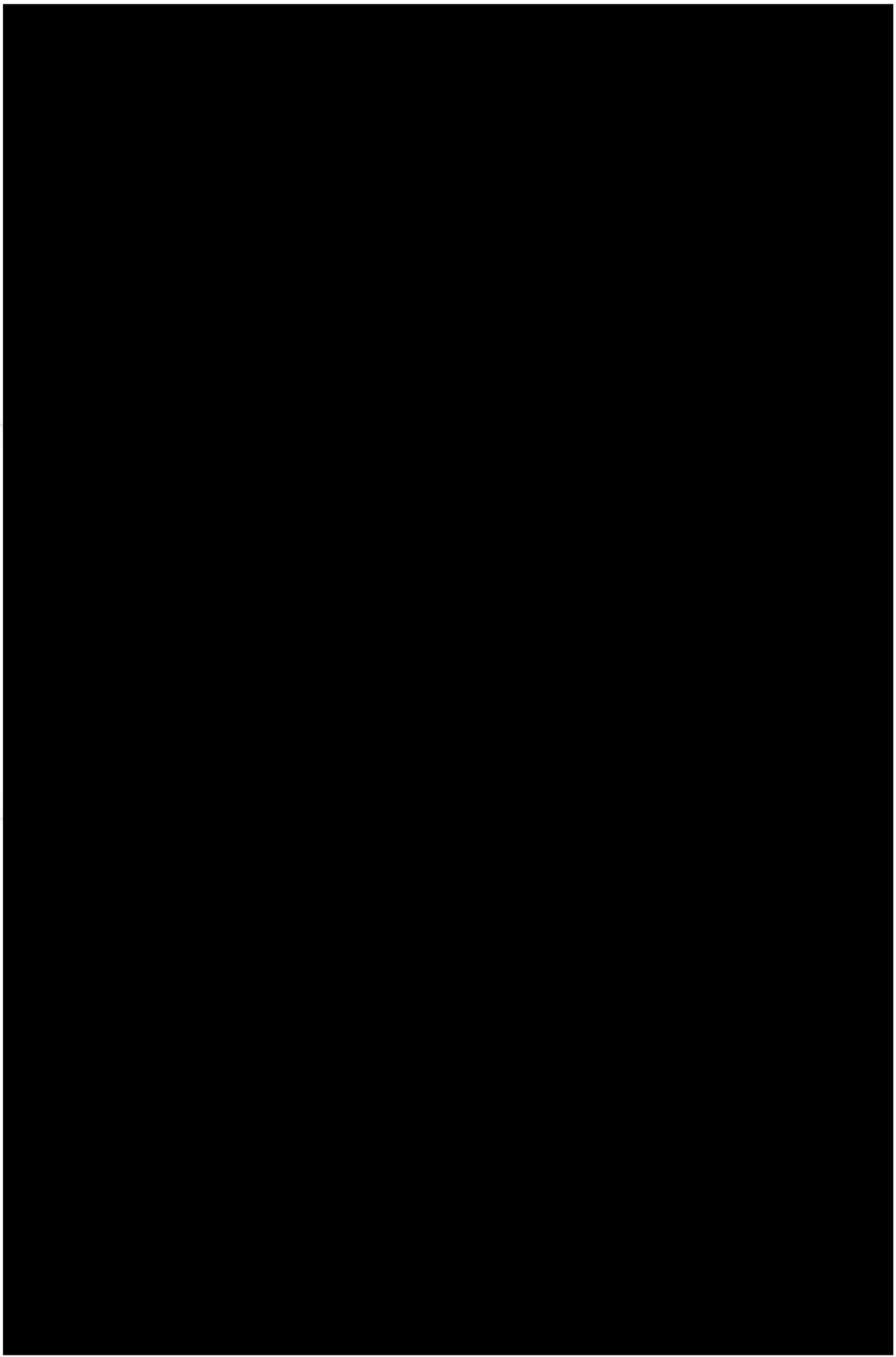
[redacted]





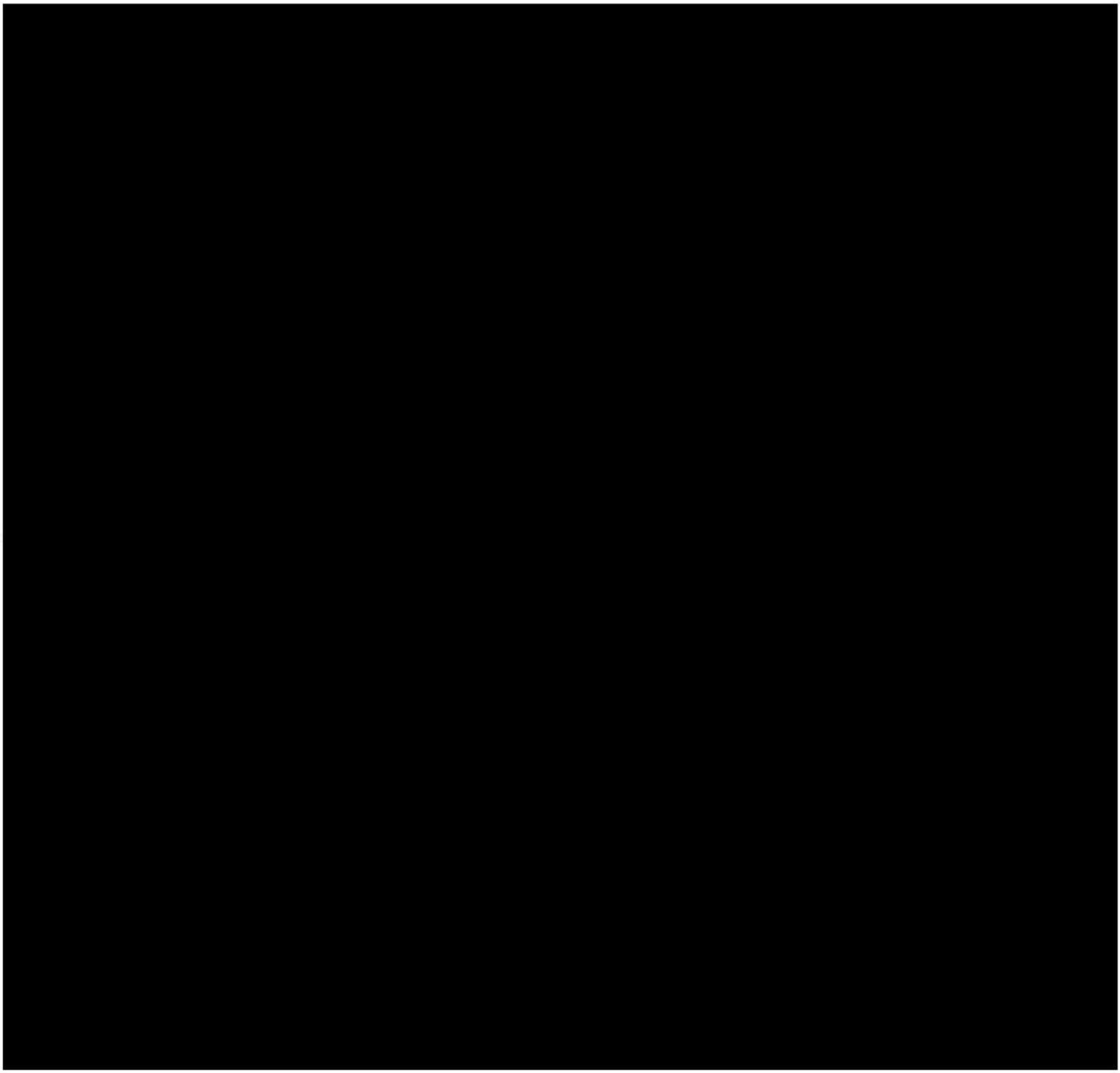






Celebrating 20 Years of OGTR
2001 - 2021

[redacted]



[redacted]

From: OGTR CDES <OGTR.CDES@health.gov.au>
Sent: Thursday, 28 September 2023 3:08 PM
To: [redacted]
Cc: [redacted]
Subject: Re: Self replicating RNA [SEC=OFFICIAL]

Dear [redacted]

Thank you for your query regarding regulation of Replicate Bioscience's self-amplifying RNA product RBI-1000 under the *Gene Technology Act 2000* (the Act).

The Gene Technology Regulator (the Regulator) has considered a number of self-amplifying RNA products to date and determined that they are regulated under the Act, based on their biological features. Information located regarding RBI-4000 (e.g., patent # US 11,730,804) indicates that the backbone vector encodes a modified alphavirus genome wherein the viral structural proteins have been replaced by coding sequence for the desired polypeptide. On this basis, these products would be considered GMOs and clinical trial of RBI-1000 would require a licence from the Regulator. The type of licence would depend on the method of administration and whether any shedding of the product from trial participants is likely to occur.

If RBI-1000 was generated in a different manner to that noted above, we would be happy to review details of its construction methodology and provide further advice. Please contact us at ogtr.cdes@health.gov.au if you have further questions.

Kind regards,

[redacted]

[redacted]
Evaluator – Contained Dealings Evaluation Section

Office of the Gene Technology Regulator | Evaluation Branch
Australian Government, Department of Health and Aged Care
T: [redacted] | E: [redacted]
Location: 11th Floor Scarborough House, Atlantic Street, Woden Town Centre, ACT 2606
PO Box 9848, Canberra ACT 2601, Australia

The Department of Health and Aged Care acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.

From: [redacted]
Sent: Saturday, 23 September 2023 7:45 AM
To: OGTR Applications <OGTR.Applications@health.gov.au>
Subject: Self replicating RNA

Dear Sir/Madam

I am writing on behalf of Replicate Bioscience. We are considering running our Phase 1/2 study of our novel targeted immunotherapeutic against endocrine resistance in ER+ breast cancer (RBI-1000) in Australia and thus keenly interested in better understanding the OGTR scope.

RBI-1000 is a fully synthetic self-replicating RNA delivered in a lipid nanoparticle (LNP). The synthetic backbone vector has had all viral structural proteins removed and replaced with the genes of interest (to delay or reverse endocrine resistance in ER+ breast cancer). The non-structural protein sequences, which enable the RNA to be copied within the cell by encoding a replicase, are only copied for the first ~4-6hours after the RNA enters the cell, until an irreversible maturation (autocatalytic) event occurs, after which only the target genes are reproduced. The compound uses the same LNP as our lead compound, RBI-4000, which is currently in clinical testing in the US (NCT06048770).

As part of our IND filing in the US for RBI-4000 we demonstrated that the srRNA-LNP had no infectivity potential (no ability to transfer genetic material to other cells as there are no viral structural proteins, and no creation of viral like particles that can transmit the srRNA). It is not an organism, nor does it enter the nucleus.

We would appreciate any chance to meet with the OGTR reviewers to discuss whether OGTR considers this program as requiring a DNIR License. If so, we would appreciate your feedback on what data might be compelling to demonstrate that srRNA vaccines are not an organism as defined by the Gene Technology Act.

We truly appreciate any guidance you can provide.

With thanks,

[redacted]

[redacted]

REPLICATE

www.replicatebioscience.com
11558 Sorrento Valley Rd, Suite 6
San Diego, CA 92121

[redacted]

[redacted]

From: OGTR CDES
Sent: Wednesday, 21 June 2023 2:14 PM
To: [redacted]
Subject: Classification of an mRNA vaccine - 2023-06-21 [SEC=OFFICIAL]

Good afternoon [redacted]

Sorry I missed your call earlier, please feel free to call back if you have further questions. This email is to follow up on our conversation yesterday regarding mRNA vaccines and provide more information. The following information should not be considered legal advice. Whether an mRNA vaccine is classified as a GMO depends on the specifics of the product in question. Some mRNA vaccines are considered GMOs and others are not.

In general terms, if the mRNA vaccine meets the definition of an 'organism' listed in the *Gene Technology Act 2000* (the Act) it will be considered a GMO. Section 10 of the Act defines an organism as a biological entity that is viable; or capable of reproduction; or capable of transferring genetic material. Section 10 of the Act defines an organism as a biological entity that is viable; or capable of reproduction; or capable of transferring genetic material.

There are two examples of mRNA COVID-19 vaccines currently available in Australia that are not considered GMOs. A hypothetical example that would be considered a GMO is a lipid nanoparticle encapsulated self-amplifying mRNA vaccine, as it is capable of reproduction and transferring genetic material.

We would be happy to provide more specifically tailored information if you are able to provide additional details of the product in question.

Kind regards,

[redacted]

Evaluator – Contained Dealings Evaluation Section
Evaluation Branch

Office of the Gene Technology Regulator
Australian Government, Department of Health and Aged Care

T: [redacted] E: [redacted]
Location: Level 11, Scarborough House, Atlantic Street, Phillip, ACT 2606
PO Box 9848, Canberra ACT 2601, Australia

The Department of Health and Aged Care acknowledges First Nations peoples as the Traditional Owners of Country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.

Australian Government

Department of Health and Aged Care
Office of the Gene Technology Regulator

[redacted]

[redacted]

MINUTES OF THE
GENE TECHNOLOGY TECHNICAL ADVISORY COMMITTEE
18 December 2023 videoconference

About these Minutes

These minutes summarise discussions during the 37th videoconference of the Gene Technology Technical Advisory Committee (GTTAC), held on 18 December 2023. They reflect key elements of the discussion, matters agreed and actions arising, and are not intended to be a verbatim record of the meeting.

[redacted]

[redacted]

[redacted]

[redacted]

Agenda Item 5. DNIR 683 – Clinical trial of genetically modified alphavirus replicon-based vaccine for the prevention of COVID-19 (Novotech (Australia) Pty Limited)

An officer from OGTR provided an overview of the RARMP prepared for licence application DNIR 683. The Regulator sought advice from GTTAC on the following issues:

- Does the risk assessment identify all plausible risk scenarios by which the proposed dealings could potentially give rise to risks relating to the health and safety of people or the environment?
- Does the committee agree that, given the genetic modifications made to the Venezuelan equine encephalitis virus (VEEV), the risks associated with the GMO are negligible?
- Is there additional relevant information that should be considered?
- Does the committee agree with the overall conclusion of the RARMP?

The Chair thanked the presenter and invited GTTAC to ask questions or seek clarification.

GTTAC discussed the sensitivity of the assay used to assess the presence of mRNA in tissues and recommended that the OGTR seek clarification from the applicant.

GTTAC noted one study [redacted] and queried whether pregnant women were excluded from the trial. Members were advised that trial participants would be [redacted] In addition, members were advised that a condition regarding the use of effective contraception for at least 30 days following treatment would be included in the licence.

GTTAC discussed the self-amplifying nature of the GMO. Members considered the capacity of the modified mRNA to transfer between cells and advised that there is little evidence suggesting it could replicate in other cells. Members discussed the composition of [redacted] the vaccine and its capacity to impact tissue and intracellular distribution of the GMO. GTTAC suggested that the OGTR address this in the RARMP, noting that it would be unlikely to change the conclusion of the risk assessment.

[redacted]

GTTAC agreed to the following resolutions:

- The risk assessment describes all plausible risk scenarios by which the proposed dealings could give risk to risks relating to the health and safety of people and the environment
- Given the genetic modifications made to the Venezuelan equine encephalitis virus, the risks associated with the GMO are negligible
- The Committee recommended that the office clarify the nature and sensitivity of the assay used to analyse mRNA in tissues.
- The Committee suggested that the office address the potential impact of the composition of the [redacted] on the tissue and intracellular distribution of the GMO in the RARMP but noted this is unlikely to impact the risk characterisation.
- The Committee asked that the wording in Paragraph 61 of the RARMP be checked and revised as appropriate.
- The Committee agreed with the overall conclusion of the RARMP.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Australian Government

Department of Health

Office of the Gene Technology Regulator

MINUTES OF THE
GENE TECHNOLOGY TECHNICAL ADVISORY COMMITTEE
16 December 2019 videoconference

About these Minutes

These minutes are intended to summarise discussion during the 18th videoconference of the Gene Technology Technical Advisory Committee (GTTAC), held on 16 December 2019. They reflect key elements of the discussion, outcomes, matters agreed and actions arising, and are not intended to be a verbatim record of the meeting.

[redacted]

[redacted]

[redacted]

Item 4. DNIR-606 - Clinical Study GO-004: An International Phase 1/2 Study of GRT-C901/GRT R902, a Neoantigen Cancer Vaccine, in Combination with Immune Checkpoint Blockade for Patients with Advanced Solid Tumors (Peter MacCallum Cancer Centre)

An officer from OGTR gave a presentation on the draft Risk Assessment and Risk Management Plan (RARMP) for licence application DNIR-606, advising that the application is to conduct a first-in-human clinical trial using two personalised vaccines, to target tumour-specific peptides displayed on the patient's cancer, in combination with drugs to improve the patient's immune response to the tumour. The risk assessment did not identify substantive risks associated with the proposed dealings.

The Regulator sought specific advice from GTTAC on the following issues:

- Is there any additional relevant information that should be considered?
- Does the committee agree that, given the genetic modifications made to the Venezuelan equine encephalitis virus, the risks associated with GRT-R902 are negligible?
- Does the draft risk assessment identify all plausible risk scenarios by which the proposed study could give rise to risks to the health and safety of people or the environment?
- Does the committee agree with the overall conclusions of the risk assessment?

GTTAC sought clarification regarding whether GRT-R902 is a genetically modified organism (GMO). OGTR clarified that GRT-R902 (GMO 2), is considered a GMO, noting that it meets the definition of an organism in the legislation because it is capable of transferring genetic material.

GTTAC suggested the RARMP should avoid terminology such as 'viral shedding' or 'infectious particles' in relation to GMO 2 (e.g. paragraphs 42 and 43), as the virus cannot replicate and therefore infectious particles cannot be shed. Instead, members suggested wording such as 'escape of input vectors', or similar.

[redacted]

[redacted]

GTTAC agreed that recombination is a possibility for GMO 2, but it is very unlikely and any risks would be negligible.

OGTR advised GTTAC that GRT-C901 (GMO 1) has low homology with human adenoviruses so recombination is very unlikely. The risk of interaction between GMO 1 and a wild type adenovirus is further reduced because the GMOs are being injected and are unlikely to reach the gut or respiratory tract where adenoviruses are found. Members added that adenovirus vectors have been used numerous times in human vaccine trials and have a history of safe use.

[redacted]

GTTAC sought clarification regarding the use of safety equipment during preparation and administration of the GMO, including whether it would be a requirement to use a respirator (paragraph 125 in the draft RARMP). OGTR clarified that the applicant proposed to use a respirator, but that the risk assessment considered there was no risk basis to require this, noting GMO preparation would be done in a biological safety cabinet.

GTTAC discussed whether tumour biopsy samples should be treated as containing GMOs (paragraph 122 in the draft RARMP). The OGTR advised that the risk assessment found that tumour samples were unlikely to contain the GMOs. Members added that tumour samples are always treated with appropriate precautions, however they suggested the RARMP could consider this further.

GTTAC queried whether staff administering Ipilimumab immediately following administration of the GMOs would be required to undertake appropriate training (paragraphs 86 and 87 in the draft RARMP), in the context of possible leakage of GMOs from the injection site. Members queried whether the sentence 'All site personnel will be instructed on the proper handling of [the GMOs]' in the RARMP captured staff administering non-GMO injections and the OGTR agreed to check this.

GTTAC suggested ensuring consistency between the text, tables and figures that describe the GMOs. Specifically, GTTAC suggested the RARMP should clarify whether the T7 promoter is part of the introduced cassette or within the E1 region or another region of the GMOs (Tables 1 and 2 of the draft licence). Members added that the T7 promoter was only relevant in the case of GMO 2.

OGTR reminded GTTAC to dispose of the agenda item in its entirety to ensure no confidential commercial information is disclosed.

<u>Resolutions:</u>

- The committee agrees with the overall conclusions of the RARMP
- The committee did not identify any additional information that should be considered
- The RARMP identifies all plausible risk scenarios
- [redacted]
- [redacted]
- The Regulator should further consider whether tumour samples should also be treated as per GMOs

[redacted]

[redacted]

From: [redacted]
Sent: Tuesday, 19 December 2023 5:12 PM
To: [redacted]
Subject: FW: just fyi - mRNA vaccines vs saRNA vaccines [SEC=OFFICIAL]

From: [redacted]
Sent: Monday, 18 December 2023 3:36 PM
To: [redacted]
Subject: just fyi - mRNA vaccines vs saRNA vaccines [SEC=OFFICIAL]

Hi all

Some of you will have received this from me already. There was discussion of this at GTTAC today.

https://www.cell.com/trends/biotechnology/fulltext/S0167-7799(23)00154-3

Comes et al. 2023 Rise of the RNA machines – self-amplification in mRNA vaccine design. Trends in Biotechnology 41: 1417-1429

The diagram was helpful to me, noting that the caption refers to the 'saRNA' as a 'propagation-deficient replicon'

Kind regards

[redacted]

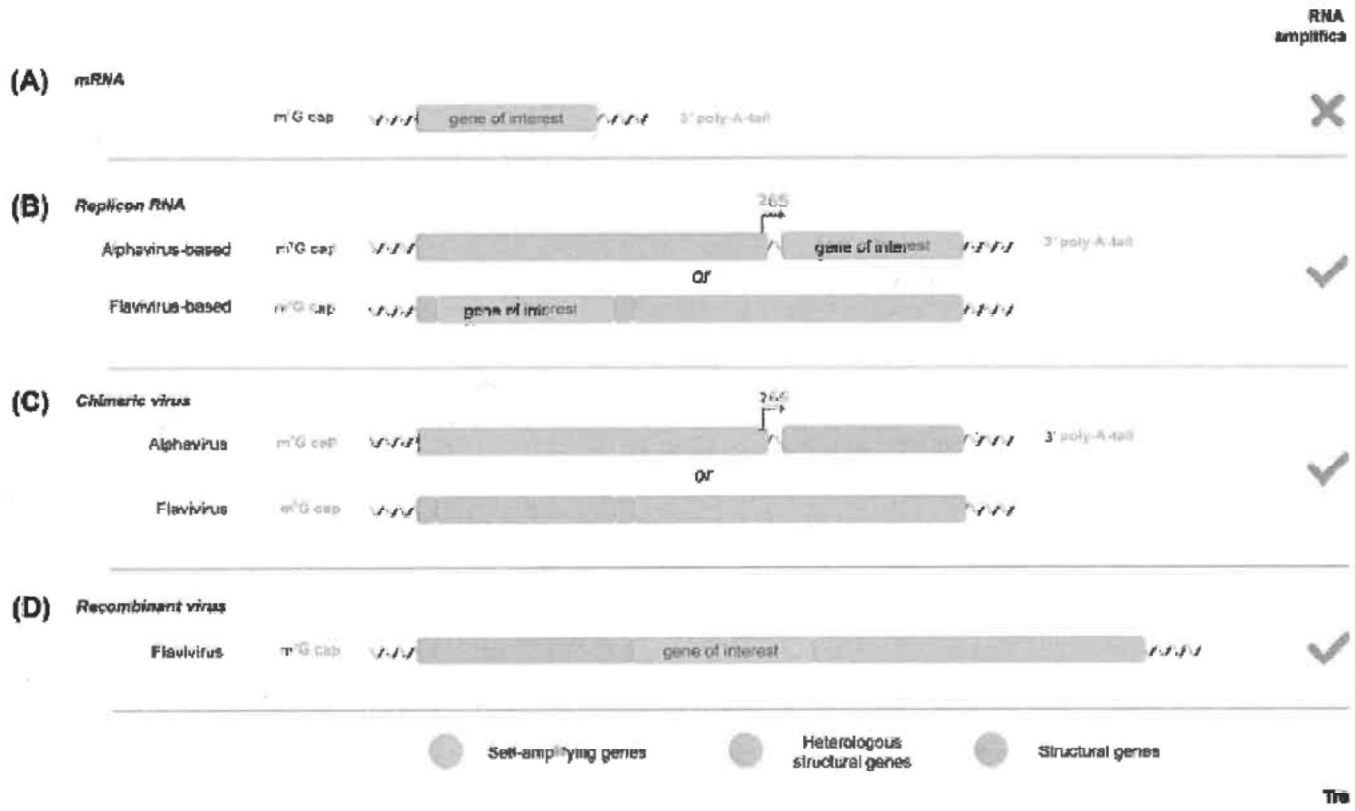


Figure I Schematic overview of (viral) nucleic acid vectors.

Hide caption

(A) An mRNA molecule contains the coding sequence of the gene of interest (GOI) flanked by a 5' m^7G Similar to the mRNA vector, (B) virus-based replicons encode the GOI but also self-amplification genes mRNA and replicon vectors are propagation-deficient as they do not encode a complete structural gen chimeric and (D) recombinant virus vectors that encode a complete (heterologous) structural gene cas propagation, not limiting transduction of the viral vector to a single cell.

[redacted]

From: [redacted]
Sent: Wednesday, 13 December 2023 4:08 PM
To: [redacted]
Cc: O'MULLANE, Matthew; [redacted]
Subject: FYI: Review: Rise of the RNA machines – self-amplification in mRNA vaccine design [SEC=OFFICIAL]
Attachments: Comes et al. 2023 Rise of the RNA machines – self-amplification in mRNA vaccine design.pdf

I already sent this paper to a handful of people in the office, but then it got circulated in a journal club. The paper has a nice diagram comparing and contrasting the different vaccine types (Fig 1).

These are being referred to as self-amplifying (m)RNAs (saRNA) but another perspective on describing/categorising it is that it is a crippled RNA viral genome (non-structural genes) with a mRNA (vaccine target coding region) added.

Cheers

[redacted]

-----Original Message-----
From: [redacted]
Sent: Tuesday, 12 December 2023 6:08 PM
To: [redacted]
Subject: Review: Rise of the RNA machines – self-amplification in mRNA vaccine design

REMINDER: Think before you click! This email originated from outside our organisation. Only click links or open attachments if you recognise the sender and know the content is safe.

Fyi - the next generation of vaccines

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4. *Classification of previous clinical trials*

- **DNIR-606 (D19-1298082): Previously you have decided that GMO2 in DNIR-606 should be regulated as a GMO- In this instance the vaccine was a self-amplifying mRNA encapsulated in a lipid nanoparticle. [redacted] that this vaccine met the definition of a GMO in the *Gene Technology Act 2000*. This was based on the fact that this viral mRNA may be considered to have an innate capacity to transfer its genetic material by recombination with a wild type alphavirus (although highly unlikely as alphaviruses only rarely recombine and the parent virus, which would be the most likely to recombine, is not present in Australia) or by complementation by a helper virus (may be possible by related alphaviruses in Australia).**

- [redacted]