July 23, 2021

Electronic Submission

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

This petition for administrative action is submitted on behalf of CAALM, the Coalition Advocating for Adequately Licensed Medicines ("Petitioner") pursuant to 21 C.F.R. § 10.30 and related relevant provisions of the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act to request that the Commissioner of Food and Drugs (the "Commissioner") require that the vaccine manufacturers provide the FDA with the data outlined in the "Actions Requested" section below before approval of any COVID-19 vaccine.

The Food and Drug Administration (FDA) has granted Emergency Use Authorizations (EUAs) to three COVID-19 vaccines, enabling rapid, and widespread vaccine rollout across the United States. These EUAs do not have any built-in expiration date, and therefore vaccines can continue to be lawfully distributed under EUA even after a future date when a public health emergency no longer exists.

Approximately seven months have passed since the first EUAs were granted, and two vaccine manufacturers now seek licensure (approval) and have submitted Biologics License Applications (BLAs). Other manufacturers have indicated similar intentions, as well as intentions for EUAs for additional pediatric populations.

We believe the FDA should not prematurely grant a license to any COVID-19 vaccine until all necessary efficacy and safety studies are completed and substantial evidence demonstrates the benefits of an individual COVID-19 vaccine product outweigh the harms for the indicated, recipient population. We are concerned that the premature licensure of a COVID-19 vaccine can seriously undermine public confidence in regulatory authorities, particularly if long-term safety issues were to emerge following licensure.

In this petition, we outline **efficacy and safety measures that must be met before serious consideration is given to granting a BLA of any COVID-19 vaccine**. These measures include:

1. **Completing at least 2 years of follow-up** of participants originally enrolled in pivotal clinical trials, even if the trials were unblinded and now lack a placebo control. All vaccine manufacturer phase 3 trials were already designed with this planned duration.

2. Ensuring, prior to including in the list of populations for which a vaccine is approved, that there is **substantial evidence of clinical effectiveness that outweighs harms in special populations** such as: infants, children, and adolescents; those with past SARS-CoV-2 infection; immunocompromised; pregnant women; nursing women; frail older adults; and individuals with cancer, autoimmune disorders, and hematological conditions.
3. Requiring thorough **safety assessment of spike proteins** being produced in-situ by the body tissues following vaccine administration, and spike proteins' full biodistribution, pharmacokinetics, and tissue specific toxicity.
4. Completion of **vaccine biodistribution studies** from administration site and safety implications of mRNA translation in distant tissues.
5. **Thorough investigation of all severe adverse reactions reported following COVID-19 vaccination**, such as deaths, reported in the United States and global pharmacovigilance systems.
6. Assessment of **safety in individuals receiving more than two doses.**
7. **Inclusion of gene delivery and therapy experts in the Vaccines and Related Biological Products Advisory Committee (VRBPAC)**, in recognition of the fact that the novel COVID vaccines work on the premise of gene delivery, in contrast to conventional vaccines.
8. **Enforcing stringent conflict of interest requirements** to ensure individuals involved in data analysis and BLA-related decision making processes have no conflict of interests with vaccine manufacturers.

A COVID-19 vaccine BLA should be approved when—and only when—substantial evidence demonstrates the benefits of a specific product outweigh the harms for the indicated, recipient population.

This means that the following are **invalid reasons** to approve a COVID-19 vaccine:

- **To ensure vaccines are accessible after the public health emergency has ended.** COVID-19 vaccines granted an emergency use authorization (EUA) can be lawfully used after the expiry of the SARS-CoV-2 public health emergency declaration. (This is made clear by the many products for Ebola and Zika viruses which still have active EUAs.[1])

- **To ensure adequate access to vaccines across the population.** A BLA is not necessary to assure access to COVID-19 vaccines. Unlike normal licensing, in which widespread use of a drug or vaccine follows approval, EUAs for COVID-19 vaccines have enabled, and continue to enable, their widespread use. Ensuring access to vaccines is irrelevant to the considerations for issuance of a BLA because broad access to COVID-19 vaccines has already been accomplished.

- **To enable vaccine mandates.** Consideration of vaccine mandates is outside of FDA's purview. Furthermore, a mandate should only be considered once the evidentiary conditions are met for a BLA (demonstrating that benefits outweigh harms).

- **To bolster public confidence.** Like mandates, approving a medical product in order to bolster public confidence is backward logic and is outside the FDA's purview. Approving before substantial evidence that population-based evidence of clinical effectiveness is superior to harms may contribute to public wariness and hesitancy, not only about COVID-19 vaccines, but other vaccines and public health authorities more broadly. An approval may bolster public confidence, but it is not a valid reason to approve.

Regardless of any legitimacy of each of the above reasons, none provides grounds to approve a COVID-19 vaccine.

The widespread use of a COVID-19 vaccine under EUA, particularly for a limited amount of time, also is not a valid reason to approve a product. Even if vaccine recipients are followed up within observational studies, such studies may have important design biases and flaws, and their conclusions, especially concerning clinical effectiveness outcomes, may not be reliable.

Premature FDA approval of any COVID-19 vaccine could negatively impact the health and safety of US residents, with global ramifications considering the international importance of FDA decisions. It also could set a precedent of lowered standards for future vaccine approvals. For these reasons and due to the compelling need to ensure the safety and efficacy of any COVID-19 vaccine licensed by the FDA and to allow Petitioner the opportunity to seek emergency judicial relief should the instant Petition be denied, it is respectfully requested that FDA act on the instant Amended Petition by July 30, 2021.

I. ACTIONS REQUESTED

Petitioner request that the FDA, prior to granting any license for a COVID-19 vaccine:

1. Confirm, in revised Guidance, that the FDA expects a minimum of 2 years of follow-up of participants enrolled in pivotal clinical trials, even if trials are unblinded and lack a placebo control.

2. Require data demonstrating substantial evidence of clinical effectiveness that outweighs harms, in all special populations, as a condition of consideration of including these populations among the indicated populations. Special populations include: infants, children, and adolescents; those with past SARS-CoV-2 infection; immunosuppressed individuals; those with history of or current cancer; individuals with hematological disorders or autoimmune diseases; pregnant or nursing women; and frail older adults.

3. Require data on the safety and pharmacokinetic profiles of the spike protein.

4. Require data from biodistribution studies investigating the actual COVID-19 vaccines.

5. Require data from pharmacovigilance systems in the US and globally documenting a thorough investigation of serious adverse events, carried out by independent, impartial individuals.

6. Clarify in revised Guidance that safety data from individuals receiving more than 2 vaccine doses must be submitted.

7. Ensure the inclusion of experts in gene therapy in the VRBPAC.

8. Ensure that the analysis of data and decisions regarding any COVID-19 vaccine BLA application are informed by experts with no financial or research relationships with any vaccine manufacturers within the last 36 months, both within FDA and amongst the composition of the VRBPAC.

II. STATEMENT OF GROUNDS

Here, in the order as above, we set out the rationale for each requested action.

1. **Confirm, in revised Guidance, that the FDA expects a minimum of 2 years of follow-up of participants enrolled in pivotal clinical trials, even if trials are unblinded and lack a placebo control. Rationale:**
    a. Requiring at least 2 years is consistent with the 2 year follow-up duration prospectively proposed by the manufacturers when they registered their ongoing phase 3 trials of COVID-19 vaccines (Moderna: NCT04470427, Pfizer: NCT04368728, Janssen: NCT04505722) and consistent with the June 2020 FDA guidance on COVID-19 vaccines which stated participants should be followed for COVID-19 outcomes for "as long as feasible, ideally at least one to two years."[2]
    b. Important adverse event signals can be detected in clinical trials. This is true despite enrolling tens of thousands of participants, which is still too few to assess rare adverse events. For example, a serious blood clot occurring in the phase 3 Janssen clinical trial led to an initial trial pause in October 2020.[3]
    c. Two year follow-up from trials allows the detection of commonly experienced longer-term adverse effects that may not manifest until many months following vaccination.
    d. Two year follow-up from trials would also allow for more detailed assessment of infection, re-infection, infectiousness, and the monitoring of immune response over time, among all vaccinated participants.
    e. The quality of data collection in clinical trials can be expected to be superior to passive data collection systems like the Vaccine Adverse Event Reporting System (VAERS). Therefore, trials of at least 2 years duration provide a valuable chance to develop a more complete understanding of the adverse event profile in the general population as well as in specific groups, such as individuals of

reproductive age, immunocompromised individuals, and different age groups, including adolescents and young children.

f. The quality of data on adverse events during an ongoing trial can be improved while the trial is ongoing (e.g., improving the range of types of adverse events that are systematically assessed), as and when evidence from other data sources (e.g., pre-clinical or pharmacovigilance) show any trends or indicate specific types of adverse events of special interest.
g. Finally, the expectation of at least 2 years of follow-up prior to BLA also carries the advantage of longer-term data collection from other available sources (e.g., MedWatch/VAERS, V-safe, Vaccine Safety Datalink, FDA-CMS, BEST & PRISM, VA Electronic Health Records & data warehouse, Department of Defense DMSS, and Genesis HealthCare (Brown University & NIH-National Institute of Aging), as well as other medical claims databases).

2. **Require data demonstrating substantial evidence of clinical effectiveness that outweighs harms, in all special populations, as a condition of consideration of including these populations among the indicated populations. Special populations include: infants, children, and adolescents; those with past SARS-CoV-2 infection; immunosuppressed individuals; those with history of or current cancer; individuals with hematological disorders or autoimmune diseases; pregnant or nursing women; and frail older adults. Rationale:**
    a. The efficacy and safety of medicines often differs amongst populations such as healthy young adults vs. older adults, men vs. women, or SARS-CoV-2 survivors vs. never-exposed individuals.
    b. For example, the relative risks of SARS-CoV-2 infection, hospitalization, and death are considerably lower in infants, children, and adolescents in comparison to adults.[4,5]
    c. For example, individuals who experienced past SARS-CoV-2 infection (which are now believed to be a significant minority of many subpopulations[6]) are likely to have immunity to subsequent infections for as long or longer than immunity conferred by vaccine,[7–10] and may also be at heightened risk for adverse effects.[11–14]
    d. The ongoing phase 3 trials of COVID-19 vaccines (Moderna: NCT04470427, Pfizer: NCT04368728, Janssen: NCT04505722) largely (or wholly) excluded the following important populations in which there is reason to believe the effects of the product may differ from the populations enrolled in the trial:
        i. Infants, children, and adolescents
        ii. Those with past SARS-CoV-2 infection
        iii. Those who are immunosuppressed
        iv. Those with history of or current cancer
        v. Those with hematological disorders
        vi. Those with autoimmune diseases
        vii. Those who are pregnant or nursing
        viii. Frail older adults (including those living in nursing homes)

e. The question is not simply whether there is efficacy, but how much efficacy exists in these populations, what kind of efficacy (e.g. reduction in risk of symptomatic COVID-19 vs. reduction in risk of hospitalization or death), and do efficacy advantages outweigh potential harms in these populations.
f. Before these special populations can be considered for inclusion amongst the approved indicated populations, data demonstrating substantial evidence of clinical effectiveness that outweighs harms in these specific populations, are needed.

3. Require data on the safety and pharmacokinetic profiles of the spike protein.
Rationale:

a. In-situ production of SARS-CoV-2 spike protein is the target mechanism of action of all COVID-19 vaccines with an EUA at present. Therefore, the safety profile of spike protein itself (i.e., in the absence of virus) must be thoroughly understood in the range of populations on the indications list.
b. Recently, evidence of systemic circulation of spike protein or its components in subjects post-immunization was reported.[15] All studies we are aware of to date raise concerns about the safety of spike protein,[16–28] and the concentration of circulatory spikes was correlated to the disease severity in COVID-19 patients.[29]
c. Required studies must, at a minimum, address these concerns:
    i. Coagulopathy issues, including blood clots, hemorrhage, thrombocytopenia, heart attack, and strokes. According to the VAERS, as of May 21, 2021, there have been a total of 1,222 reports of thrombocytopenia/low platelets; and 6,494 (112 in 0-24 year-olds) reports of blood clots/strokes.
    ii. Reproductive issues, including menstrual irregularities, reduced fertility, miscarriages, and preterm births. According to VAERS, as of May 21, 2021, there were 511 reports of miscarriage and 522 reports of uterine hemorrhage (including 88 in women older than 50 years). The vaccines induce the generation of antibodies to attack spike protein, which are genetically similar to proteins produced by the placenta.[30] To date, no vaccine sponsors have conducted immunologic studies of spike protein involvement with proteins involved in placental development.
    iii. Carcinogenesis. There is preliminary and theoretical evidence that the spike protein may promote cancer.[31,32] Considering the potential for annual booster vaccinations, COVID-19 vaccines should be treated similarly to medication taken for chronic conditions on a long term basis. Carcinogenic potential is important to characterize.
    iv. Transmission of spike protein (or its fragments) from vaccinated individuals, such as through breast milk and associated risk in neonates and infants. According to the UK Medicines & Healthcare products Regulatory Agency, there are 921 reports of exposure via breast milk following AstraZeneca's vaccine and 215 reports following Pfizer's vaccine.

v. Neurological disorders, including Guillain-Barré syndrome, acute disseminated encephalomyelitis, transverse myelitis, encephalitis, myelitis, encephalomyelitis, meningoencephalitis, meningitis, encephalopathy, demyelinating diseases, and multiple sclerosis.
vi. Cardiac issues, including myocardial infarction, myocarditis and pericarditis, among others. According to the VAERS, as of May 21, 2021, there have been a total of 1,598 reports of heart attacks (24 reported in 0-24 year-olds; 501 resulted in death).
vii. Autoimmune diseases, including thyroiditis and diabetes mellitus, immune thrombocytopenia, autoimmune hepatitis, primary biliary cholangitis, systemic sclerosis, autoimmune disease for skeletal muscles (myasthenia gravis, myositis such as polymyositis, dermatomyositis, or other inflammatory myopathies)
viii. Studies should be conducted in individuals of both sexes[33] and all ages. We cannot assume that the effects of spike protein are the same across populations of all ages, sex, and across pre-existing conditions.

4. **Require data from biodistribution studies investigating the actual COVID-19 vaccines. Rationale:**
    a. Data from the biodistribution studies submitted by Moderna and Pfizer suggests that the vaccines distribute widely in the body, including to the liver, brain, heart, lung, adrenals, ovaries, and testes, among many other tissues.[34,35] (**See Tables 1a, 1b, and 2 below for studies R-[?]-0072 and 185350 submitted by Pfizer and study 5002121 submitted by Moderna.**)
    b. However these were not studies of the currently authorized products: Pfizer's BNT162b2, Moderna's mRNA-1273, or Janssen's Ad26.COV2.S.[34–36]
    c. Instead of presenting novel biodistribution studies of the COVID-19 vaccine formulations, sponsors presented substitute studies to FDA for an EUA during the pandemic.[34–36]
    d. Therefore, novel biodistribution studies investigating the actual COVID-19 vaccines are necessary.
    e. Biodistribution studies would be required for any small molecule pharmaceutical drug submitted for approval (i.e. New Drug Application), and should be conducted on the COVID-19 vaccines as well as these novel vaccines which work on the premise of gene delivery--very different to conventional vaccines.
    f. Biodistribution studies help inform an understanding of vaccine transfection to various tissues (away from injection site) spurring various distant tissues to produce spike proteins and consequent autoimmune response against the body's cells. These studies will therefore help enhance our understanding of the nature of potential short and long term adverse events. At this point in time, in which other data sources exist to characterize short term harms of COVID-19 vaccines with an EUA, the utility of biodistribution studies to characterize long term adverse effects and better understand potential mechanism(s) of action of short and long term harms, remains critically important.

g. Necessary studies must, at a minimum, address these concerns related to biodistribution, as well as the effects of vaccines in the body:
    i. The need to know basic pharmacokinetic parameters, including absorption, distribution, metabolism, and excretion (ADME).
    ii. Effects of multiple doses. ADME may change depending on dose and cumulative dose and should be investigated. This is more important than usual as the whole purpose of all COVID-19 vaccines with an EUA at present is to change the body's way of processing spike protein, and therefore repeated injections should result in different rates of clearance of spike protein from the blood, and different rates of immune attack on spike protein producing cells.
    iii. The impact of body mass index (size of deltoid muscle) and vaccine distribution away from injection site, implications for dose estimation for lean or younger age groups or frail older adults.
    iv. The duration of the studies must be sufficient to fully understand the complete distribution and elimination of the injected vaccine and its carrier and other constituents. For example, data from the substitute study submitted for Pfizer's vaccine (**see Tables 1a, 1b, and 2 below for studies R-[?]-0072 and 185350 submitted by Pfizer and study 5002121 submitted by Moderna**) showed levels of drug product increasing at the 48 hour mark, but it is unknown what occurred after 48 hours as this was apparently the study cut off.[37]
    v. Potential side effects (safety review) in those organs/tissues with a detectable proportion of injected vaccine (antigen or novel excipients) from the circulatory system.

5. **Require data from pharmacovigilance systems in the US and globally documenting a thorough investigation of serious adverse events, carried out by independent, impartial individuals. Rationale:**
    a. A major testament to the overall short-term safety of a medical product is the absence of serious adverse events (SAEs) when administered to millions. COVID-19 vaccines have now been administered to hundreds of millions of individuals, and it is vital that all reports of SAEs are thoroughly investigated to determine whether the vaccine played any role in the SAE.
    b. The most serious of all SAEs is death, and a CDC webpage on VAERS discusses 4,863 reports of death after COVID-19 vaccination reported between December 14, 2020 and May 24, 2021.[38] CDC states that:
        i. "CDC follows up on any report of death to request additional information to learn more about what occurred and to determine whether the death was a result of the vaccine or was unrelated."
        ii. "CDC and FDA physicians review each case report of death as soon as notified and CDC requests medical records to further assess reports."

iii. "A review of available clinical information, including death certificates, autopsy, and medical records has not established a causal link to COVID-19 vaccines."[38]

c. However, the FDA has stated that VAERS staff do not contact family members to learn more about the deaths. It stated: "Because the VAERS system is not designed to determine causality of adverse events, there is not a mechanism to follow-up with families for additional details. The determination of the cause of death is done by the certifying official who completes the death certificate or the pathologist who conducts the autopsy."[39]
d. Regulators in other countries have conducted detailed case investigations (e.g. Norway's investigation of 100 deaths amongst frail elderly following COVID-19 vaccination[40,41]).
e. FDA must require evidence of a thorough investigation into deaths and other SAEs—investigations that include contacting families to obtain a full medical history and personal accounts (in the case of deaths) and those who experienced the adverse event (in the case of other SAEs). Event adjudication, as done on data safety monitoring boards, must be in place in order to carry out detailed case investigations, and must be carried out by independent, impartial individuals.

6. **Clarify in revised Guidance that safety data from individuals receiving more than 2 vaccine doses must be submitted by vaccine manufacturers. Rationale:**
   a. There is wide speculation that COVID-19 vaccines may become offered as annual vaccines, much like influenza vaccines, and regulators have already released guidance to this effect.[42]
   b. Some manufacturers, such as Pfizer and Moderna, have indicated that a third dose may be necessary within the first 12 months. Other manufacturers may present similar claims in the future.[43]
   c. The safety profile of multiple doses, possibly more than 70 doses across an average lifetime, must be considered at the time of licensure. Phase 3 trial data make clear that the safety profile differs by dose (e.g. dose 2 of the Pfizer and Moderna vaccines induce more severe systemic adverse events than dose 1).[44,45]
   d. Information on the types and severity of adverse events that emerge following the administration of additional doses is necessary to better characterize long term safety.

7. **Ensure the inclusion of experts in gene therapy in the VRBPAC.** Rationale:
   a. The COVID-19 vaccines produced by Pfizer, Moderna, and Janssen (as well as AstraZeneca, CanSinoBio (China) and Gamaleya Research Institute (Russia)) are gene based vaccines. Their mechanism of action differs substantially from all other vaccines that have been used on populations globally, as these novel vaccines work on the premise of gene delivery, and may therefore be considered a type of gene therapy. These gene based vaccines involve entering the cell, where the overwhelming majority of critical body activities occur, and utilizing

the host's cells to produce spike protein. This is an entirely different mechanism than that utilized by traditional vaccines such as inactivated, attenuated, subunit or protein-based (that are not intended to invade cells). Therefore, there is a need to consider safety with the informed perspectives of those with expertise in gene therapies.

8. **Ensure that the analysis of data and decisions regarding any COVID-19 vaccine BLA application are informed by experts with no financial or research relationships with any vaccine manufacturers within the last 36 months, both within FDA and amongst the composition of the VRBPAC. Rationale:**
    a. The public interest weighs strongly in favor of the evaluation of data and all decision making to be performed by competent individuals with independence from vaccine manufacturers (institutions that stand to gain or lose from a BLA decision on a COVID-19 vaccine). Disclosure requirements should be at least as stringent, if not more, than what is expected for writing a manuscript in a medical journal—namely, disclosure of relationships within the last 36 months, as requested by the International Committee of Medical Journal Editors (ICMJE). Insisting on this level of disclosure, and transparency of the disclosures, can publicly demonstrate the independence of the FDA's decision making process.[46]

Table 1a. Pfizer study report R-[?]-0072, biodistribution study submitted by Pfizer to Japanese regulator (PMDA).

2.6.5.5A. PHARMACOKINETICS: ORGAN DISTRIBUTION		**Test Article: modRNA encoding luciferase in LNP** **Report Number: R-[redacted]-0072**
Species (Strain):	Mice (BALB/c)	
Sex/Number of Animals:	Female/3 per group	
Feeding Condition:	Fed ad libitum	
Vehicle/Formulation:	Phosphate-buffered saline	
Method of Administration:	Intramuscular injection	
Dose (mg/kg):	1 µg/hind leg in gastrocnemius muscle (2 µg total)	
Number of Doses:	1	
Detection:	Bioluminescence measurement	
Sampling Time (hour):	6, 24, 48, 72 hours; 6 and 9 days post-injection	

Time point	**Total Mean Bioluminescence signal (photons/second)**		**Mean Bioluminescence signal in the liver (photons/second)**
	Buffer control	**modRNALuciferase in LNP**	**modRNALuciferase in LNP**
6 hours	1.28×10^{5}	1.26×10^{9}	4.94×10^{7}
24 hours	2.28×10^{5}	7.31×10^{8}	2.4×10^{6}
48 hours	1.40×10^{5}	2.10×10^{8}	Below detection[a]
72 hours	1.33×10^{5}	7.87×10^{7}	Below detection[a]
6 days	1.62×10^{5}	2.92×10^{6}	Below detection[a]
9 days	7.66×10^{4}	5.09×10^{5}	Below detection[a]

LNP = Lipid nanoparticle; modRNA = Nucleoside modified messenger RNA.
a. At or below the background level of the buffer control.

Source: Japan PMDA (PDF page 15).[37]

Table 1b. Pfizer study report 185350, biodistribution study submitted by Pfizer to Japanese regulator (PMDA).

2.6.5.5B. PHARMACOKINETICS: ORGAN DISTRIBUTION CONTINUED

Test Article: [^{3}H]-Labelled LNP-mRNA formulation containing ALC-0315 and ALC-0159
Report Number: 185350

Species (Strain):	Rat (Wistar Han)
Sex/Number of Animals:	Male and female/3 animals/sex/timepoint (21 animals/sex total for the 50 µg dose)
Feeding Condition:	Fed ad libitum
Method of Administration:	Intramuscular injection
Dose:	50 µg [^{3}H]-08-A01-C0 (lot # NC-0552-1)
Number of Doses:	1
Detection:	Radioactivity quantitation using liquid scintillation counting
Sampling Time (hour):	0.25, 1, 2, 4, 8, 24, and 48 hours post-injection

Sample	Mean total lipid concentration (µg lipid equivalent/g (or mL) (males and females combined)							% of administered dose (males and females combined)						
	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h
Adipose tissue	0.057	0.100	0.126	0.128	0.093	0.084	0.181	--	--	--	--	--	--	--
Adrenal glands	0.271	1.48	2.72	2.89	6.80	13.8	18.2	0.001	0.007	0.010	0.015	0.035	0.066	0.106
Bladder	0.041	0.130	0.146	0.167	0.148	0.247	0.365	0.000	0.001	0.001	0.001	0.001	0.002	0.002
Bone (femur)	0.091	0.195	0.266	0.276	0.340	0.342	0.687	--	--	--	--	--	--	--
Bone marrow (femur)	0.479	0.960	1.24	1.24	1.84	2.49	3.77	--	--	--	--	--	--	--
Brain	0.045	0.100	0.138	0.115	0.073	0.069	0.068	0.007	0.013	0.020	0.016	0.011	0.010	0.009
Eyes	0.010	0.035	0.052	0.067	0.059	0.091	0.112	0.000	0.001	0.001	0.002	0.002	0.002	0.003
Heart	0.282	1.03	1.40	0.987	0.790	0.451	0.546	0.018	0.056	0.084	0.060	0.042	0.027	0.030
Injection site	128	394	311	338	213	195	165	19.9	52.6	31.6	28.4	21.9	29.1	24.6
Kidneys	0.391	1.16	2.05	0.924	0.590	0.426	0.425	0.050	0.124	0.211	0.109	0.075	0.054	0.057
Large intestine	0.013	0.048	0.093	0.287	0.649	1.10	1.34	0.008	0.025	0.065	0.192	0.405	0.692	0.762
Liver	0.737	4.63	11.0	16.5	26.5	19.2	24.3	0.602	2.87	7.33	11.9	18.1	15.4	16.2
Lung	0.492	1.21	1.83	1.50	1.15	1.04	1.09	0.052	0.101	0.178	0.169	0.122	0.101	0.101
Sample	**Total Lipid concentration (µg lipid equivalent/g [or mL]) (males and females combined)**							**% of Administered Dose (males and females combined)**						
	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h
Lymph node (mandibular)	0.064	0.189	0.290	0.408	0.534	0.554	0.727	--	--	--	--	--	--	--
Lymph node (mesenteric)	0.050	0.146	0.530	0.489	0.689	0.985	1.37	--	--	--	--	--	--	--
Muscle	0.021	0.061	0.084	0.103	0.096	0.095	0.192	--	--	--	--	--	--	--
Ovaries (females)	0.104	1.34	1.64	2.34	3.09	5.24	12.3	0.001	0.009	0.008	0.016	0.025	0.037	0.095
Pancreas	0.081	0.207	0.414	0.380	0.294	0.358	0.599	0.003	0.007	0.014	0.015	0.015	0.011	0.019
Pituitary gland	0.339	0.645	0.868	0.854	0.405	0.478	0.694	0.000	0.001	0.001	0.001	0.000	0.000	0.001
Prostate (males)	0.061	0.091	0.128	0.157	0.150	0.183	0.170	0.001	0.001	0.002	0.003	0.003	0.004	0.003
Salivary glands	0.084	0.193	0.255	0.220	0.135	0.170	0.264	0.003	0.007	0.008	0.008	0.005	0.006	0.009
Skin	0.013	0.208	0.159	0.145	0.119	0.157	0.253	--	--	--	--	--	--	--
Small intestine	0.030	0.221	0.476	0.879	1.28	1.30	1.47	0.024	0.130	0.319	0.543	0.776	0.906	0.835
Spinal cord	0.043	0.097	0.169	0.250	0.106	0.085	0.112	0.001	0.002	0.002	0.003	0.001	0.001	0.001
Spleen	0.334	2.47	7.73	10.3	22.1	20.1	23.4	0.013	0.093	0.325	0.385	0.982	0.821	1.03
Stomach	0.017	0.065	0.115	0.144	0.268	0.152	0.215	0.006	0.019	0.034	0.030	0.040	0.037	0.039
Testes (males)	0.031	0.042	0.079	0.129	0.146	0.304	0.320	0.007	0.010	0.017	0.030	0.034	0.074	0.074
Thymus	0.088	0.243	0.340	0.335	0.196	0.207	0.331	0.004	0.007	0.010	0.012	0.008	0.007	0.008
Thyroid	0.155	0.536	0.842	0.851	0.544	0.578	1.00	0.000	0.001	0.001	0.001	0.001	0.001	0.001
Uterus (females)	0.043	0.203	0.305	0.140	0.287	0.289	0.456	0.002	0.011	0.015	0.008	0.016	0.018	0.022
Whole blood	1.97	4.37	5.40	3.05	1.31	0.909	0.420	--	--	--	--	--	--	--
Plasma	3.97	8.13	8.90	6.50	2.36	1.78	0.805	--	--	--	--	--	--	--
Blood:Plasma ratio[a]	0.815	0.515	0.550	0.510	0.555	0.530	0.540	--	--	--	--	--	--	--

Source: Japan PMDA (PDF page 16).[37]

Table 2. Modern study report 5002121, biodistribution study submitted by Moderna to Japanese regulator (PMDA).

表 2.6.4.4-3　雄性 Sprague Dawley ラットに mRNA-1647 100 µg を単回筋肉内接種したときの各組織における薬物動態パラメータ

Matrix	mRNA Construct	T_{max} (h)[a]	C_{max} (ng/mL)[a]	$AUC_{(0-t)}$ (ng × h/mL)[a,b]	$T_{1/2}$ (h)[a,c]	$AUC_{(0-t)}$ Ratio (Tissue/Plasma)[d]	$AUC_{(0-t)}$ Ratio (Tissue/Plasma) Average
Bone marrow	gB	NC	NC	NC	NC	NC	NR
	gH	8.0	0.254 ± 0.0871	7.85 ± 2.03	NC	0.316	
	gL	8.0	0.224 ± 0.0920	2.78 ± 1.03	NC	0.119	
	UL128	8.0	0.292 ± 0.120	3.53 ± 1.33	NC	0.147	
	UL130	NC	NC	NC	NC	NC	
	UL131A	8.0	0.186 ± 0.0829	2.05 ± 0.912	NC	0.0825	
Brain	gB	NC	NC	NC	NC	NC	NR
	gH	24.0	0.0800 ± 0.0491	2.19 ± 1.08	NC	0.0880	
	gL	2.0	0.0360 ± 0.0360	0.144 ± 0.144	NC	0.00615	
	UL128	2.0	0.0340 ± 0.0340	0.136 ± 0.136	NC	0.00564	
	UL130	NC	NC	NC	NC	NC	
	UL131A	NC	NC	NC	NC	NC	
Distal lymph node	gB	8.0	108 ± 101	1,460 ± 1,110	31.6	64.1	62.8
	gH	8.0	110 ± 102	1,490 ± 1,130	36.2	59.8	
	gL	8.0	117 ± 109	1,460 ± 1,200	30.6	62.6	
	UL128	8.0	125 ± 117	1,620 ± 1,290	32.1	67.1	
	UL130	8.0	129 ± 121	1,630 ± 1,330	27.9	64	
	UL131A	8.0	114 ± 108	1,470 ± 1,190	28.5	59.2	
Eye	gB	2.0	4.72 ± 2.77	26.7 ± 13.6	NC	1.18	1.24
	gH	2.0	3.92 ± 2.19	37.6 ± 11.0	NC	1.51	
	gL	2.0	3.23 ± 1.84	29.2 ± 9.75	NC	1.25	
	UL128	2.0	3.91 ± 2.19	34.5 ± 12.2	NC	1.43	
	UL130	2.0	3.61 ± 2.14	21.3 ± 11.0	NC	0.838	
	UL131A	2.0	3.43 ± 1.96	31.1 ± 10.2	NC	1.26	
Heart	gB	NC	NC	NC	NC	NC	NR
	gH	8.0	0.548 ± 0.107	9.94 ± 1.85	NC	0.400	
	gL	8.0	0.220 ± 0.0907	2.96 ± 1.05	NC	0.127	
	UL128	8.0	0.276 ± 0.113	4.49 ± 1.51	NC	0.186	
	UL130	NC	NC	NC	NC	NC	
	UL131A	8.0	0.312 ± 0.0896	3.71 ± 1.02	NC	0.150	
Injection site, muscle	gB	2.0	1,770 ± 803	27,100 ± 4,880	13.5	1190	939
	gH	2.0	1,720 ± 828	26,100 ± 4,700	17.1	1050	
	gL	2.0	1,310 ± 638	20,900 ± 3,720	15.2	893	
	UL128	2.0	1,620 ± 720	25,300 ± 4,090	14.9	1050	
	UL130	2.0	1,630 ± 777	24,500 ± 4,240	13.8	961	
	UL131A	8.0	427 ± 210	12,100 ± 2,830	15.0	487	
Jejunum	gB	NC	NC	NC	NC	NC	NR
	gH	8.0	0.0800 ± 0.0490	2.06 ± 1.04	NC	0.0827	
	gL	2.0	0.0700 ± 0.0429	0.720 ± 0.472	NC	0.0308	
	UL128	NC	NC	NC	NC	NC	
	UL130	NC	NC	NC	NC	NC	
	UL131A	NC	NC	NC	NC	NC	
Kidney	gB	NC	NC	NC	NC	NC	NR
	gH	NC	NC	NC	NC	NC	
	gL	NC	NC	NC	NC	NC	
	UL128	NC	NC	NC	NC	NC	
	UL130	NC	NC	NC	NC	NC	
	UL131A	NC	NC	NC	NC	NC	
Liver	gB	2.0	2.16 ± 1.21	8.65 ± 4.83	NC	0.381	0.499
	gH	2.0	2.12 ± 0.982	16.8 ± 4.15	NC	0.674	
	gL	2.0	1.30 ± 0.432	11.0 ± 2.37	NC	0.470	
	UL128	2.0	2.00 ± 0.814	13.7 ± 3.72	NC	0.570	
	UL130	2.0	1.87 ± 1.01	7.46 ± 4.04	NC	0.293	
	UL131A	2.0	1.99 ± 0.928	13.9 ± 4.04	NC	0.562	
Lung	gB	NC	NC	NC	NC	NC	NR
	gH	8.0	0.442 ± 0.130	8.04 ± 1.96	NC	0.323	
	gL	8.0	0.274 ± 0.0984	3.45 ± 1.12	NC	0.148	
	UL128	8.0	0.340 ± 0.129	5.40 ± 1.74	NC	0.224	
	UL130	8.0	0.188 ± 0.188	2.07 ± 2.07	NC	0.0812	
	UL131A	8.0	0.310 ± 0.111	4.86 ± 1.49	NC	0.196	

Proximal lymph nodes	gB	2.0	260 ± 121	5,850 ± 949	33.5	257	201
	gH	8.0	206 ± 51.6	4,860 ± 722	38.2	195	
	gL	2.0	175 ± 81.9	3,460 ± 538	36.3	148	
	UL128	8.0	246 ± 66.6	5,190 ± 875	32.8	215	
	UL130	8.0	252 ± 67.2	5,240 ± 881	35.7	206	
	UL131A	2.0	225 ± 106	4,600 ± 719	32.2	185	
Spleen	gB	2.0	7.36 ± 3.81	460 ± 52.9	46.9	20.2	13.4
	gH	24.0	5.63 ± 1.28	371 ± 39.5	83.0	14.9	
	gL	8.0	3.83 ± 1.04	196 ± 21.0	68.2	8.36	
	UL128	24.0	4.87 ± 1.22	297 ± 34.8	68.8	12.3	
	UL130	8.0	5.03 ± 1.41	288 ± 33.0	64.9	11.3	
	UL131A	2.0	5.10 ± 2.64	277 ± 33.1	46.2	11.2	
Stomach	gB	NC	NC	NC	NC	NC	NR
	gH	8.0	0.110 ± 0.0696	3.49 ± 1.59	NC	0.140	
	gL	8.0	0.0800 ± 0.0499	2.07 ± 1.19	NC	0.0886	
	UL128	24.0	0.102 ± 0.0648	2.85 ± 1.47	NC	0.118	
	UL130	NC	NC	NC	NC	NC	
	UL131A	24.0	0.0980 ± 0.0634	2.53 ± 1.39	NC	0.102	
Testes	gB	2.0	1.16 ± 0.719	4.64 ± 2.88	NC	0.204	0.209
	gH	2.0	1.11 ± 0.480	5.52 ± 2.20	NC	0.222	
	gL	8.0	0.420 ± 0.335	6.08 ± 3.73	NC	0.260	
	UL128	2.0	0.946 ± 0.397	4.73 ± 1.85	NC	0.196	
	UL130	2.0	0.682 ± 0.442	2.73 ± 1.77	NC	0.107	
	UL131A	2.0	0.872 ± 0.380	4.54 ± 1.85	NC	0.183	

Abbreviations: gB = glycoprotein B; gH = glycoprotein H; gL = glycoprotein L; IM = intramuscular; NC = not calculable (insufficient data points above the lower limit of quantitation); NR = not reported (some constructs measured all samples as below limit of quantitation).

[a] T_{max} and $T_{1/2}$ data reported as the mean; C_{max} and $AUC_{(0-t)}$ data reported as the mean ± standard error.

[b] For the bone marrow, brain, jejunum, heart, liver, lung, stomach, and testes, $AUC_{(0-t)}$ was calculated using less than 3 quantifiable mean concentrations and therefore is an estimate.

[c] Due to the lack of a distinct elimination phase in plasma, the $T_{1/2}$ of the mRNA constructs could not be calculated; however, the $T_{1/2}$ was estimated to range from 2.7 to 3.8 hours.

[d] For $AUC_{(0-t)}$ Ratio, samples listed as NC were not calculable because all samples were below limit of quantitation.

Source: Report 5002121 Amendment 1 (Appendix 8, Table 2 and Table 3)

Source: Japan PMDA (PDF page 7).[47]

III. ENVIRONMENT IMPACT

The petitioner hereby states that the relief requested in this petition will have no environmental impact and therefore an environmental assessment is not required under 21 C.F.R. Sections 25.30 and 25.31.

IV. ECONOMIC IMPACT

Economic impact information will be submitted upon request of the commissioner.

V. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

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