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13 August 2021

[redacted]

[redacted]
Ref: H202106950

Dear [redacted]

Response to your request for official information

Thank you for your request under the Official Information Act 1982 (the Act) to the Ministry of Health (the Ministry) on 5 June 2021 for:

> *"… OIA copies of all documents discovered by the Crown in the Nga Kaitiaki Tuku Iho v Minister of Health High Court proceedings in whatever non-confidential form they are available. As these documents are already readily accessible for the crown I would be grateful if you would please provide them by reply."*

Information within scope of this request is itemised in Appendix 1 of this letter and copies of the documents are enclosed. The table in Appendix 1 outlines the grounds under which I have decided to withhold information. Where information is withheld, this is noted in the document itself.

I trust this information fulfils your request. Under section 28(3) of the Act you have the right to ask the Ombudsman to review any decisions made under this request. The Ombudsman may be contacted by email at: info@ombudsman.parliament.nz or by calling 0800 802 602.

Please note that this response, with your personal details removed, may be published on the Ministry website at: www.health.govt.nz/about-ministry/information-releases/responses-official-information-act-requests.

Yours sincerely

Chris James
Group Manager
Medsafe

Appendix 1: Documents for release

#	Date	Title	Decision on release
1	6 September 2013	Delegation of Director-General's powers	Released in full.
2	11 September 2013	Delegation of powers by the Minister of Health.	
3	20 September 2013	Delegation of Minister's powers by the Director-General of Health	
4	21 October 2020	New Medicine Application cover letter	Released with some information withheld under the following sections of the Act: • section 9(2)(a) to protect the privacy of natural persons; • section 9(2)(b)(ii) where its release would likely unreasonably prejudice the commercial position of the person who supplied the information; and • section 9(2)(ba)(i) to protect information that is subject to an obligation of confidence and making it available would likely prejudice the supply of similar information, or information from the same source.
5	4 November 2020	Terms of Reference Medsafe COVID-19 Vaccine Advisory Group	Released in full.
6	13 November 2020	New Medicine Application cover letter	Released with some information withheld under the following sections of the Act: • section 9(2)(a); • section 9(2)(b)(ii); and • section 9(2)(ba)(i).
7	January 2021	New Medicine Application Evaluation Report – Quality	Released with some information withheld under the following sections of the Act: • section 6(b)(ii) as its release would prejudice information entrusted to the Government of New Zealand on a basis of confidence by any international organisation; and • section 9(2)(b)(ii).

#	Date	Title	Decision on release
8	January 2021	New Medicine Application Evaluation Report – New Excipient (ALC-0135)	Released with some information withheld under the following sections of the Act: • section 9(2)(b)(ii); and • section 9(2)(g)(ii).
9	January 2021	New Medicine Application Evaluation Report – New Excipient (ALC-0159)	
10	January 2021	New Medicine Application Evaluation Report – Clinical	
11	20 January 2021	Science and Technical Advisory Team – Request for Information	Released with some information withheld under section 9(2)(g)(ii) .
12	28 January 2021	New Medicine Application Evaluation Report – Non-Clinical	Released with some information withheld under the following sections of the Act: • section 6(b)(ii); • section 9(2)(b)(ii); and • section 9(2)(g)(ii).
13	28 January 2021	Memo: Referral to the Medicines Assessment Advisory Committee – Comirnaty (COVID-19 mRNA vaccine) (Pfizer-BioNTech) 0.5 mg/mL concentrate for injection (TT50-10853)	Released with some information withheld under section 9(2)(g)(ii) .
14	28 January 2021	Letter regarding the application for consent	Released with some information withheld under the following sections of the Act: • section 9(2)(a); and • section 9(2)(g)(ii).
15	3 February 2021	Medicines Assessment Advisory Committee minutes and recommendations - 109th meeting on 2 February 2021	
16	N/A	New medicine application form: Prescription medicine	Released with some information withheld under the following sections of the Act: • section 9(2)(a); and • section 9(2)(b)(ii).
17	N/A	New Medicine Application Evaluation Report– Risk Management Plan	Released with some information withheld under section 9(2)(b)(ii) .
18	N/A	New Medicine Application Evaluation Report – Quality (Attachments)	Released with some information withheld under the following sections of the Act: • section 6(b)(ii); and • section 9(2)(b)(ii).

DELEGATION OF POWERS BY THE

DIRECTOR-GENERAL OF HEALTH

under section 41 of the State Sector Act 1988

The powers and functions of the Director-General of Health under the statutes and regulations administered by the Ministry of Health are set out in Appendix 1 of this document.

The column of the table in Appendix 1 headed "Persons Exercising Existing Delegation" lists those powers and functions delegated by the Director-General of Health immediately prior to this delegation instrument coming into force, and the classes of office holder who exercised those delegated powers.

The column of the table in Appendix 1 headed "Delegation Confirmed or Created" lists the delegations of the Director-General's powers and functions either confirmed or created by this delegation instrument, and the classes of office holder to whom those powers are now delegated.

The classes of office holders to whom the Director-General's functions and powers are delegated by this delegation instrument are authorised to exercise the powers and functions from the date of the signing of this delegation.

For the avoidance of doubt, the delegation of a power to a class of office holder shall include delegation of that power to a person validly acting in that class.

All previous delegations of the Director-General of Health relating to the powers and functions set out in Appendix 1 are hereby revoked.

The powers hereby delegated by me remain subject to my general control.

These delegations are made on 6th September 2013 under section 41 of the State Sector Act 1988.

Kevin Woods
Director-General of Health

Section	Summary of function/responsibility/power	Persons Exercising Existing Delegation	Delegation Confirmed or Created
	STATUTES		
	MEDICINES ACT 1981		
2 "Medical Officer of Health"	The Director-General is a "Medical Officer of Health" for the purposes of the Act.		
2 "Licensing authority"	The Director-General is a "licensing authority" for the purposes of the Act.		
15 Appointment of officers	(2) The Director-General may from time to time appoint any person, not being an officer of the Public Service, as an officer, either in a part or full time capacity, for the purposes of this Act.	Group Manager, Medsafe	H
	(3) Any appointment under subsection (2) of this section may be made either generally for the purposes of this Act or for any specified purpose, or for the exercise of any specified power or function of an officer under this Act, or for any specified period; and may be made in respect of New Zealand generally or in respect of any specified area or areas		
	(4) The Director-General must fix the remuneration to be paid to officers appointed under this section.	Group Manager, Medsafe	H
16 Exercise of Powers by D-G and other officers	(2) Subject to subsection (1) of this section, each Medical Officer of Health employed in the Ministry of Health, and every other officer of the Ministry of Health, must exercise the powers and functions conferred on him by this Act subject to the direction and control of the Director-General of Health and of every other officer of the Ministry of Health to whom s/he is subordinate.		
21(1)(c) 21(2)(l) Applications for Minister's consent	Section 21 provides the Director-General must in the first instance receive applications for the Minister's consent for distribution of a "new medicine" under s20 The Director-General may require authentication (and may specify the manner of such authentication) of translations of reports on medicines (concerning safety, efficacy, etc) required for the purposes of s21(2)(i)-(k).	Group Manager, Medsafe	H, I

Section	Summary of function/responsibility/power	Persons Exercising Existing Delegation	Delegation Confirmed or Created
	STATUTES		
	MEDICINES ACT 1981		
21(3) Changed medicine notice may be deemed application for s20 consent	(3) In the case of a medicine to which section 20 of this Act applies by virtue of subsection (1) of that section, the notice deposited with the Director-General under section 24 of this Act shall, subject to subsections (4) and (5) of this section, be a sufficient application for the consent of the Minister under section 20.	Group Manager, Medsafe	H, I, Ia, Ib
21(4) D-G may require samples	(4) At any time before the publication of a notice in the *Gazette* signifying the consent of the Minister to the distribution of a medicine in respect of which an application under section 20 of this Act has been made, the Director-General may, by notice in writing given to the person in whose name the application was made, require that person to supply - (a) Such samples of the medicine; and (b) Such further information or particulars concerning the medicine, or the manufacture, intended sale, distribution, or advertising of the medicine,— as the Director-General may specify in the notice.	Manager, Product Regulation, Medsafe; Manager, Compliance Manager, Medsafe	H, I, Ia, Ib
21(5) D-G may require verification	(5) The Director-General may, if s/he thinks fit, require any person to verify by statutory declaration any statement in an application made, or in any further information or particulars supplied, under this section and signed by that person.	Group Manager, Medsafe	H
23(2) D-G must receive application for provisional consent	(2) The Director-General must in the first instance receive applications for provisional consent for a new medicine to be sold, supplied or distributed on a limited basis.	Group Manager, Medsafe	H
24(1) and (1A) Distribution of changed medicines restricted	The Director-General must receive a changed medicines notice from the manufacturer or importer of the medicine in New Zealand, setting out the particulars required by s24(2), where a material change to an approved medicine is made by a manufacturer of that medicine. (1A) The DG must receive the accompanying fee for the notice	Group Manager, Medsafe	H
24(3) D-G may consent to supply	The Director-General may give his/her prior written consent to a person selling or supplying any medicine in respect of which there has been a material change, earlier the expiry of 90 days after which the changed medicines notice has been deposited with the Director-General.	Manager, Product Regulation, Medsafe; Group Manager, Medsafe	H, I, Ia, Ib

Section	Summary of function/responsibility/power	Persons Exercising Existing Delegation	Delegation Confirmed or Created
	STATUTES		
	MEDICINES ACT 1981		
24(4) D-G may require further information or particulars	Within 45 days after the receipt of any notice in accordance with subsection (1) of this section, the Director-General may, by written notice to the importer or manufacturer, require the importer or manufacturer to supply such further information or particulars, or such samples, as the Director-General may require with respect to any matter set out in the importer's	Evaluation Team Advisors	H, I, Ia, Ib
24(5) D G may refer CMN to Minister	If the Director-General, after considering the particulars, information, or samples required by or under subsection (1) or subsection (4) of this section, at any time within the period specified in subsection (3) of this section considers - (a) That the change is of such a character or degree that the medicine ought not, without the consent of the Minister,— (i) To be distributed in New Zealand; or (ii)To be represented, recommended, advertised, or labelled in the terms set out in the notice; or (b) That s/he is insufficiently informed, for the purposes of paragraph (a) of this subsection, about - (i) The strength, quality, purity, safety, or efficacy of the medicine; or (ii)The methods of manufacture of, or the facilities for testing, the medicine,— the Director-General must refer the medicine to the Minister, and forthwith inform the importer or manufacturer by notice in writing that s/he has done so.	Group Manager, Medsafe	H, I
24A Assessment of qualifying new medicines	The Director-General may grant an approval under section 38I of the Hazardous Substances and New Organisms Act 1996 for the release of a qualifying new medicine if he or she— (a) has the consent of the Minister to do so; and (b) is acting under a delegation from ERMA given under section 19 of that Act.	National Director, National Health Board	R, H
24B(a) Procedure if D-G declines to grant approval	If the Director-General declines to grant an approval because the new organism is not a qualifying new medicine, then the Director-General must— (i) inform ERMA that the new medicine is not a qualifying new medicine; and (ii) provide ERMA with a copy of all information (from assessing the safety, quality, and efficacy of the new medicine) that the Director-General considers may assist ERMA in deciding whether to approve or decline the application under the Hazardous Substances and New Organisms Act 1996; and	Group Manager, Medsafe	H

Section	Summary of function/responsibility/power	Persons Exercising Existing Delegation	Delegation Confirmed or Created
	STATUTES		
	MEDICINES ACT 1981		
24D(3)(b) Special emergencies	The Director-General must approve forms in which applications may be made to the Minister for approval to distribute, sell, or advertise in a special emergency a medicine that is or contains a hazardous substance or new organism.	Group Manager, Medsafe	H
29(2) Exemption for medicine required medical practitioner	(2) Every person who, for the purposes of subsection (1) of this section (supply of new medicine by medical practitioner for treatment of particular patient), sells or supplies to any practitioner any medicine that is a new medicine by virtue of paragraph (a) of the definition of the term "new medicine" in section 3(3) of this Act before the consent of the Minister has been notified in the *Gazette* shall, as soon as practicable aftr the end of every month in which he has to sold or supplied any such medicine, report that sale or supply to the Director-General in writing, naming the practitio0ner and patient, describing the medicine, and identifying the occasion when and the place where the medicine was so sold or supplied.	Group Manager, Medsafe	H and J
30(1) Distribution for clinical trial	The Director-General must approve or disapprove clinical trials (and also the investigators who will conduct those trials) of any medicine before the medicine may be distributed for the sole purpose of obtaining clinical and scientific information with respect to its safety and efficacy.	Principal Clinical Advisor, Medsafe	H, Z, Za
30(2) Applications for distribution	The Director-General must receive applications for distribution of a medicine for clinical trial purposes under (1), and the applications must comply with s30(2)(a)-(d) and contain the particulars in s30(3).	Group Manager, Medsafe	H, Z, Za
30(4) D-G to determine application	The Director-General must determine every application for his approval under this section within 45 days after the receipt of the application, and must notify the applicant of his decision and (where he declines the application) the reasons for his decision and (where he declines the application) the rasons for his decision.	Principal Clinical Advisor, Medsafe	H, Z, Za

Section	Summary of function/responsibility/power	Persons	Delegation

Section	Summary of function/responsibility/power	Persons Exercising Existing Delegation	Delegation Confirmed or Created
	STATUTES		
	MEDICINES ACT 1981		
30(5) D-G may approve investigators	At any time after a clinical trial has been approved by the Director-General, the applicant may apply to the Director-General for the approval of an i nvestigator, notwithstanding that the name of that person did not appear in the application for approval of the clinical trial; and paragraphs (a) o (c) of subsection (2), and paragraphs (c), (d), and (g) of subsection (3), of this section apply in respect of every such application.	Principal Clinical Advisor, Medsafe	H, Z, Za
30(6) D-G may require further information	The Director-General may at any time, by notice in writing given to an applicant, require the applicant to supply such further information and particulars as s/he thinks fit relating to a clinical trial or to the identity and qualifications of an investig	Principal Clinical Advisor, Medsafe	H, Z, Za
30(7)(a), (d) Condition of distribution for clinical trial	Where approval has been given under s30, the Director-General must be informed, before the medicine is distributed, of the identifying name or mark by which the medicine may be recognised. The importer or manufacturer must - (i) Keep complete and accurate records of all quantities of the medicine supplied under this section; (ii) Keep the Director-General informed of the progress of the trial by six-monthly reports: (iii) Supply to the Director-General a copy of the results of the trial on its completion.		H, Z, Za
30(8) D-G may revoke approval	The Director-General may at any lime, by notice in writing to the applicant, revoke or suspend his/her approval of a clinical trial.	Group Manager, Medsafe	H, Z, Za
32A(1) Exemption for importation by the Crown	The Director-General may approve the importation of a medicine into New Zealand, and sale of that medicine, by the Crown, before the Minister's consent to distribution has been obtained.		
36(1), (2) Control of established medicines by D-G	(1) Without limiting subsection (5) of section 24 of this Act, if the Director-General has reason to believe that any medicine, not being a new medicine, may be unsafe or ineffective for the therapeutic purpose for which it is sold, s/he may, by notice in writing to an importer or manufacturer in New Zealand, state the reasons for his belief and require the importer or manufacturer to satify him of the safety or efficacy of that medicine.	Group Manager, Medsafe	H
	(2) If the Director-General is not satisfied, by evidence supplied to him pursuant to a notice under subsection (1) of this section or otherwise, of the safety and efficacy of a medicine to which that notice relates, s/he may at any time after the expiry	Group Manager, Medsafe	H

Section	Summary of function/responsibility/power	Persons Exercising Existing Delegation	Delegation Confirmed or Created
	STATUTES		
	MEDICINES ACT 1981		
38 Restrictions on sale of medical devices	(2) If the Director-General has reason to believe that any medical device (see s38(1) for expanded definition) may be unsafe, s/he may, by notice in writing to the importer or manufacturer in New Zealand, state the reasons for his belief, and require the importer or manufacturer to satisfy him/her of the safety of that medical device.	Group Manager, Medsafe	H
	(3) The importer or manufacturer must supply to the Director-General, within 45 days after receiving the notice under subsection (2) of this section, or such further time as the Director-General may allow, evidence of the safety of the medical device.	Group Manager, Medsafe	H
	(4) If the Director-General is not satisfied, by evidence supplied to him/her pursuant to a notice under subsection (3) of this section or otherwise of the safety of the medical device, he may at any time, within the period of 45 days following the receipt of that evidence, by a further notice under subsection (2) of this section require the manufacturer or importer to supply him with further evidence of the safety of the medical device.		H
	(6)The Director-General may exercise the powers conferred on him/her by this section from time to time with respect to different importers or manufacturers of the same kind of medical devices, and the fact that he has not exercised any of those powers in respect of a particularkind of medical device, or that he has informed any person that he is satisfied of the safety of a particular kind of medical device, does not prevent him/her from exercising any such power in respect of that kind of medical device where new information comes to his attention.	Group Manager, Medsafe	H
41(1) D-G to receive notification of untoward effects of medicines	(1) If at any time the importer or manufacturer in New Zealand of any medicine has reason to believe that any substantial untoward effects have arisen from the use of the medicine whether in New Zealand or elsewhere, the importer or manufacturer must forthwith notify the Director-General of the nature of those effects and the circumstances in which they have arisen, so far as they are known to him/her.	Principal Clinical Advisor, Medsafe	H, Z

Section	Summary of function/responsibility/power	Persons Exercising Existing Delegation	Delegation Confirmed or Created
	STATUTES		
	MEDICINES ACT 1981		
50(1), (5) D-G must receive applications for licences	(1) The Director-General or any other person designated for the purpose must receive every application for a licence. (5) If the Director-Genoral or a person authorised to receive an application under subsection (1) is satisfied that an application complies with the requirements of this section and of any regulations made under this Act that are applicable to the application, s/he must refer the application to the licensing authority.	G, L	G, L
51 D-G may issue, revoke and suspend licences	(1) Subject to subsection (2) of this section and to sections 52, 55A, and 55B, on receiving an application, the Director-General must issue a licence, in accordance with regulations made under this Act, to the applicant if s/he is satisfied in respect of all the following matters: (a) That the requirements of section 50 of this Act have been complied with (applications): (b) That, in the case of an application made by a natural person on his own behalf, the applicant is a fit and proper person to hold the licence applied for, or, in the case of an application made on behalf of a body corporate, the applicant (body corpora (c) That the applicant is not subject to any disqualification under section 83 of this Act: (d)That, in the case of an application made by a natural person on his own behalf, the applicant, or, in the case of an application made on behalf of a body corporate, every person proposed to be a responsible person for the purposes of the licence applie (e)That the premises and equipment that the applicant proposes to use are suitable and adequate for the purposes for which the licence is sought: (f)That adequate arrangements have been made or are to be made for the making, maintaining, and safekeeping of adequate records in respect of medicines that are manufactured, stored, packed, labelled, or sold in pursuance of the licence or, in the case o	G, L	G, L
	(2) Except as may be permitted by regulations made under this Act, the Director-General must not issue a licence to sell medicines by retail in respect of any premises othor than a shop that is open to the public and is situated at least 10 kilometres by	Group Manager, Medsafe	G, L
	(3) The Director-General must not decline an application for a licence under this section without first giving the applicant a reasonable opportunity to be heard.	Group Manager, Medsafe	G and L for pharmacy licences or sale of medicines licences. H and J
	(4) A licence shall be in the prescnbed form and the Director-General may place conditions on it in accordance with the Medicines Regulations.	Group Manager, Medsafe	H & J for licences to manufacture and pack medicines. G and L for pharmacy licences or sale of medicines licences.

Section	Summary of function/responsibility/power	Persons Exercising Existing Delegation	Delegation Confirmed or Created
	STATUTES		
	MEDICINES ACT 1981		
	(5) A licence to sell a medicine may be combined with a licence to pack that medicine.	Group Manager, Medsafe	H & J for licences to pack medicines. G and L for pharmacy licences or sale of medicines licences.
	(6) If in any case the Director-General is satisfied that the holder of a licence has failed or is failing to comply with any conditions attaching to the licence, s/he may— (a) Suspend the licence for such reasonable period as may be required to enable the licensing authority to consider the case; or (b) After giving the licensee a reasonable opportunity to be heard and considering any evidence adduced or submission made by the licensee, cancel the licence	Group Manager, Medsafe	H for licences to manufacture and pack medicines. G and L for pharmacy licences or sale of medicines licences.
	(6A) If the Director-General is satisfied that the holder of a licence to operate a pharmacy has failed to comply with any conditions affecting the licence, the Director-General may, instead of or as well as exercising the powers conferred by subsection (6), - (a) impose on the holder of the licence a penalty not exceeding $40,000. (b) forbid the licence holder or any person with an interest in the pharmacy from holding any interest in or operating a pharmacy for a period, not exceeding 5 years, specified by the licensing authority.	Group Manager, Medsafe	G and L
	(7) If the Director-General refuses to issue a licence, or attaches conditions to a licence, or cancels a licence under this section or under section 55A, and the applicant for the licence or the licensee requests him/her to give his reasons for such refusal, or for the attachment of such conditions, or for the cancellation of the licence, the Director-General must state his reasons in writing to that person.	Group Manager, Medsafe	H and J for licences to manufacture and pack medicines. G and L for pharmacy licences or sale of medicines licences.

Section	Summary of function/responsibility/power	Persons Exercising Existing Delegation	Delegation Confirmed or Created
	STATUTES		
	MEDICINES ACT 1981		
52(1)(a) Licence to manufacture medicines	The Director-General may grant a licence to manufacture medicines.	Group Manager, Medsafe; and Manager, Compliance Manager, Medsafe	H and J
52(1)(b)	The Director-General may grant a licence to pack and label medicines.	Team Leader, Medicines Control	H and J
52(1)(c)	The Director-General may grant a licence to sell medicines by wholesale.	Team Leader, Medicines Control	G and L
52(1)(d)	The Director-General may grant a licence to sell medicines by retail	Team Leader, Medicines Control	G and L
52(1)(e)	The Director-General may grant a licence to operate a pharmacy (power to be exercised subject to the restrictions under s55D(2), 55E and 55F and the exemption in s55G).	Team Leader, Medicines Control	G and L
54(2) D-G may require production of licence	Where a licensee has been unable to produce his/her licence for inspection (on the request of an officer), the Director-General may require the licensee to produce it at the Ministry of Health (or offices of the delegate) within 24 hours.-	Compliance Team Advisors for non-pharmacy related activities. Medicine control Advisors for licences to operate a pharmacy.	J, L, Ja, Jb, La, Y
55(1) D-G must maintain register of licences	The Director-General must maintain at his/her offices a Register of Licences granted under the Act, and such other records or registers as may be prescribed under regulations.	Group Manager, Medsafe; and Team Leader, Medicines Control	H and J for licences to manufacture and pack medicines. G and L for pharmacy licences or sale of medicines licences.

Section	Summary of function/responsibility/power	Persons Exercising Existing Delegation	Delegation Confirmed or Created
	STATUTES		
	MEDICINES ACT 1981		
55A Additional criteria to be satisfied by pharmacy operators	(1) The Director-General must not grant an application for a licence to operate a pharmacy unless s/he is satisfied that, in addition to satisfying the criteria set out in section 51(1),— (a) the applicant is a person who is qualified under any of sections 55D, 55E, or 55G, to be granted a licence to operate a pharmacy; and (b) the applicant is a person who is able to satisfy the condition set out in section 55C. (2) If the Director-General has reasonable grounds to believe that the holder of a licence to operate a pharmacy has ceased to be a person who satisfies each of the criteria set out in subsection (1), the Director-General may suspend the licence for a rea (3) If, after giving the holder of a licence to operate a pharmacy whose licence is suspended under subsection (2) a reasonable opportunity to be heard and after considering any evidence adduced or submissions made by the licensee, the Director-General is (4) If, after giving the holder of a licence to operate a pharmacy whose licence is suspended under subsection (2) a reasonable opportunity to be heard and after considering any evidence adduced or submissions made by the licensee, the Director-General is	Group Manager, Medsafe; and Team Leader, Medicines Control	G and L
55B D-G may require further information	(1) The Director-General, may for one or more of the purposes set out in subsection (2), require an applicant for a licence to operate a pharmacy to supply information additional to that contained in the application (2)The purposes referred to in subsection (1) are— (a)the determination of the nature of the interest held by any person in the pharmacy: (b)the assessment required by section 51(1)(b) (which requires an applicant who is an individual to be a fit and proper person and an applicant who is a body corporate to be of good repute): (c)the assessment required by section 55A(1). (3) The Director-General may permit the applicant to submit the further information outside the period of 30 days of the date of the request which is ordinarily required.	Group Manager, Medsafe; and Team Leader, Medicines Control	G and L
66 D-G may require information	(1) Without limiting section 63 of this Act, where the Director-General reasonably suspects that any person is in possession— (a) Of any medicine or medical device for the purpose of sale; or (b) Of any substance or article for the purpose of the manufacture, packing, sale, or supply of any medicine or medical device; or (c) Of any advertising material or labelling material for use as an advertisement or label in breach of this Act or of any regulations made under this Act, s/he may require that person to produce for his inspection, or to produce to any officer specially authorised by him/her for the purpose, any books, documents, or other records dealing with	Officers under the Medicines Act	J, L, Ja, Jb, La, Y

Section	Summary of function/responsibility/power	Persons Exercising Existing Delegation	Delegation Confirmed or Created
	STATUTES		
	MEDICINES ACT 1981		
	(2) The Director-General may make or cause to be made copies of or extracts from any such books, documents, or other records.	Officers under the Medicines Act	
74(2) D-G may issue certificate	The Director-General may issue a certificate relating to the contents of any register under the s55 of the Act or stating that on a date specified in the certificate the name of any person did not appear in the said register as a licensee, or any particulars specified in the certificate did not appear in the said register, and this may be used as sufficient evidence in proceedings.		
81(7) D-G to be notified of cancellation etc	The Director-General must receive notification by the Registrar of a court of the particulars of the cancellation of any licence, or the disqualification or endorsement of a licence under s83(1)(b) or (c)		H for licences to manufacture and pack medicines. G and L for pharmacy licences or sale of medicines licences.
83(7) Particulars of convictions	The particulars of any cancellation, disqualification, or endorsement under this section, and the particulars of the conviction relating to any of these, must be notified in writing to the Director-General by the Registrar of the Court.	Group Manager, Medsafe	H for licences to manufacture and pack medicines. G and L for pharmacy licences or sale of medicines licences.

Section	Summary of function/responsibility/power	Persons Exercising Existing Delegation	Delegation Confirmed or Created
	STATUTES		
	MEDICINES ACT 1981		
86(2), (5) D-G must public withdrawal order	(2) Where a court has ordered withdrawal of goods from circulation after conviction of a person under s61, the Director-General must cause particulars of the order and of the offence in relation to which the order was made to be published in the Gazette.	Group Manager, Medsafe	H
	(5) Where any person referred to in subsection (1) of this section is convicted of an offence against any of sections 57 (Restrictions on Advertising), 58 (Further restrictions on advertising), and 61 (Misleading Branding) of this Act, the Director-General may cause particulars of the offence and a description of the substances or articles in relation to which the offence was committed to be published in the *Gazette*.		
91(3) D-G must implement appeal decision	(3) Where the High Court or the Court of Appeal modifies a decision of the Medicines Review Committee, or substitutes a new decision, the Minister, or the Director-General, or the licensing authority, as the case may require, shall take all necessary measures to implement the decision of the Court.		
96G(2) Forms for biotechnical procedures	The Director-General must approve the form to be used to obtain the Minister's authorisation for a biotechnical procedure under s96C or 96D.		H
98 Statement by D-G	(1) The Director-General may, for the purpose of protecting the public, publish statements relating to medicines of any description or medical devices of any kind or to any matter contained or implied in advertisements, either generally or in any particular advertisement, or any class or classes of advertisements, relating to medicines of any description or medical devices of any kind. (2) Every statement published under this section is protected by qualified privilege		
99 D-G must publish lists of general sales medicines	(1) The Director-General must from time to time, in such manner as s/he thinks fit, publish a list or lists of general sale medicines lawfully sold in New Zealand, other than prescription medicines, restricted medicines, and pharmacy-only medicines.	Group Manager, Medsafe	H
107 Power to obtain information for the purposes of regulations	(2) For the purpose of enabling the making of regulations under this Act, or the giving of any notice under section 106 of this Act, the Director-General may from time to time, by notice in writing to any manufacturer or importer in New Zealand of medicines of any description, or medical devices of any kind, require the manufacturer or importer to state correctly in writing to the Director-General the nature of the ingredients or components of such medicines or devices, and the proportions or manner in which those ingredients or components are contained in them. * In this section the term ``manufacturer'', in relation to a medicine, includes a person who, as owner, packs or causes to be packed medicines of that description for sale or supply.	Group Manager, Medsafe	H

DELEGATION OF POWERS BY THE

MINISTER OF HEALTH

under section 28 of the State Sector Act 1988

The powers and functions of the Minister of Health under the statutes and regulations administered by the Ministry of Health are set out in Appendix 1 of this document.

The column of the table in Appendix 1 headed "Persons Exercising Existing Delegation" lists those powers and functions delegated by the Minister of Health immediately prior to this delegation instrument coming into force, and the classes of office holder who exercised those delegated powers.

The column of the table in Appendix 1 headed "Delegation Confirmed or Created" lists the delegations of the Minister's powers and functions either confirmed or created by this delegation instrument, and the classes of office holder to whom those powers are now delegated.

The classes of office holders to whom the Minister's functions and powers are delegated by this delegation instrument are authorised to exercise the powers and functions from the date of the signing of this delegation.

For the avoidance of doubt, the delegation of a power to a class of office holder shall include delegation of that power to a person validly acting in that class.

All previous delegations of the Minister of Health relating to the powers and functions set out in Appendix 1 are hereby revoked.

The powers hereby delegated by me remain subject to my general control.

These delegations are made on 6th September 2013 under section 28 of the State Sector Act 1988.

Hon Tony Ryall
Minister of Health

Appendix 1

Tables of the Minister of Health's Powers and functions under statutes and regulations administered by the Ministry of Health

Classes of Office Holders in the Ministry of Health

DG:	Director-General of Health
Class A:	Any Deputy Director General/National Director, National Health Board
Class B:	Director of Public Health
Class C:	Director of Mental Health
Class D:	Medical Officers of Health employed in the Ministry of Health
Class E:	Manager, Environmental and Border Health
Class F:	National Manager, Risk and Assurance
Class G:	Manager, Provider Regulation
Class H:	Group Manager, MEDSAFE
Class I:	Manager, Product Regulation, MEDSAFE
Class Ia:	Team Leaders, Product Regulation, MEDSAFE
Class Ib:	Advisors, Product Regulation, MEDSAFE
Class J:	Manager, Compliance Management, MEDSAFE
Class Ja:	Team Leaders, Compliance Management, MEDSAFE
Class Jb:	Advisors, Compliance Management, MEDSAFE
Class K:	Principal Clinical Advisor, MEDSAFE
Class L:	Team Leader, Medicines Control
Class La:	Advisors, Medicines Control
Class M:	Team Leader, HealthCERT
Class Ma:	Senior Advisors, HealthCERT
Class N:	Team Leader, Office of Radiation Safety
Class O:	Regulatory Administrators of the Office of Radiation Safety
Class P:	Deputy-Director General, Sector Capability and Implementation
Class Q:	National Director, National Health Board
Class Qa:	Director; Performance, Accountability, Monitoring and Funding; National Health Board
Class Qb:	Principal Advisor, Business Services, National Health Board
Class Qc:	Group Manager, National Collections and Reporting, National Health Board
Class Qd	Team Leader, Classifications and Terminology, NZ Cancer Registry, National Health Board
Class R:	Chief Medical Officer, Clinical Leadership Protection and Regulation
Class Ra:	Establishment Manager, New Regulators, Clinical Leadership Protection and Regulation
Class Rb:	General Manager, Cancer Control New Zealand, Clinical Leadership Protection and Regulation
Class S:	Director, National Services Purchasing
Class Sa:	Director, Intellectual Disability Compulsory Care and Rehabilitation, Disability Services
Class T:	Director, Information Group
Class U:	Deputy Director-General, Policy
Class V:	Deputy Director-General, Māori Health
Class W:	Deputy Director-General, Corporate Services
Class X:	Chief Nurse
Class Y:	Officers appointed under section 15 Medicines Act 1981
Class Z:	Manager, Clinical Risk Management, MEDSAFE

Section	Summary of function/responsibility/power	Persons Exercising Existing Delegation	Delegation(s) and Sub-Delegation(s) Confirmed or Created
	MEDICINES ACT 1981		
2(1) Definitions of "analyst" "approved laboratory, and 2(2)	The Minister has the power to approve laboratories for the purposes of the Medicines Act, by notice in the *Gazette,* subject to such terms and conditions as the Minister thinks fit, and may approve analysts to be in charge of those laboratories.	DG; Chief Medical Officer, Clinical Leadership Protection and Regulation; Group Manager, Medsafe	DG, R, H
8	The Minister may from time to time appoint such advisory or technical committees as s/he thinks fit to advise him/her for any of the purposes of this Act, and may from time to time determine the functions of any such committee.		
9(1)(3)	The Minister must (under s8) appoint an advisory committee known as the Medicines Classification Committee (MCC), to make recommendations to the Minister in respect of the classification of any medicines as prescription medicines or restricted medicines or pharmacy-only medicines under this Act. The MCC must consist of— (a) Two persons, to be nominated by the New Zealand Medical Association: (b) Two persons, to be nominated by the Pharmaceutical Society of New Zealand: (c) Two persons, being officers of the Ministry of Health, one of whom shall be appointed as chairman.		
9(2)	The Minister can refer matters relating to any of the other purposes of the Medicines Act, to the MCC, and receive advice from the MCC on such matters.		
9(5)	The Minister has the power to remove any member of the MCC on grounds of disability, neglect of duty or misconduct proved to the satisfaction of the Minister.		
9(5)	The Minister can accept a written resignation from any member of the Medicines Classification Committee.		
10(1)(2) & (3)	The Minister must establish a Medicines Review Committee (MRC) and must appoint to the MRC 6 members of whom 1 shall be appointed by the Minister as chairman, and must include at least— (a) One person with wide experience in the practice of medicine: (b) One person with wide experience in the practice of pharmacy: (c) One person with wide experience in the pharmaceutical manufacturing industry: (d) One person with wide experience in a form of chemistry other than pharmaceutical chemistry. The Minister must also appoint 1 person with wide experience in the practice of natural therapy to act as a member of the MRC whenever any matter relating to the practice of natural therapy is before the MRC		
11(1)	The Minister may appoint deputies for MRC members on grounds of incapacity by illness, absence or other sufficient cause. Deputies may only be appointed if they meet the eligibility criteria for members in s10(1)		

Section	Summary of function/responsibility/power	Persons Exercising Existing Delegation	Delegation(s) and Sub-Delegation(s) Confirmed or Created
	MEDICINES ACT 1981		
13(1)(a) & (5)	The Minister must receive reports by Medicines Review Committee into objections to recommendations made under section 22(2). The Minister may make decisions on matter to which the objection relates, following a recommendation by the MRC.		
14	The Minister must provide every committee appointed under section 8 of this Act, and the MRC, with such staff, accommodation, services, and other facilities as appear to him to be necessary or expedient for the proper performance of its functions by that	DG; Chief Medical Officer, Clinical Leadership Protection and Regulation; Group Manager, Medsafe	**DG, R and H**
16(1)	The Minister may give directions to the Director-General, Medical Officer of Health and other officers in the exercise of their powers and functions under the Medicines Act.		
20(2)	The Minister may give consent or provisional consent to selling, distribution or advertising of "new medicines". Consent may be subject to conditions, and must be notified by the Minister in the *Gazette*.	DG; Chief Medical Officer, Clinical Leadership Protection and Regulation; Group Manager, Medsafe	**DG, R and H**
20(6A)	The Minister must, after having given consent, or provisional consent to the distribution of a new medicine, give written notification of that consent to the Environmental Risk Management Authority (ERMA) established under the Hazardous Substances and New Organisms Act 1996 (HSNO Act).	DG; Chief Medical Officer, Clinical Leadership Protection and Regulation; Group Manager, Medsafe	**DG, R and H**
22(1)	After receiving an application for his or her consent to the distribution of a new medicine, the Minister must consider the particulars and information relating to the medicine submitted under section 21, and such other matters as appear to be relevant, and (as far as practicable) eigh the likely therapeutic value of the medicient against the risk of potential injury to any person.		**DG, R, H, I**
22(2)	The Minister may refer an application for consent to an appropriate committee for advice and recommendations in the event that the Minister, having complied with section 22(1), is not satisfied that s/he should grant consent.		**DG, R, H, I**
22(3)	If the committee's recommendation is to refuse consent, the Minister must notify applicant of the recommendation and any reasons for it.	DG; Chief Medical Officer, Clinical Leadership Protection and Regulation; Group Manager, Medsafe	**DG, R and H**

Section	Summary of function/responsibility/power	Persons Exercising Existing Delegation	Delegation(s) and Sub-Delegation(s) Confirmed or Created
	MEDICINES ACT 1981		
22(5)	On receipt of an objection from the applicant under subsection (4) of this section, the Minister must, before making his decision, refer the matter to the MRC, which must report on it to the Minister with a recommendation as to the decision that the Minister should make.	DG; Chief Medical Officer, Clinical Leadership Protection and Regulation; Group Manager, Medsafe	**DG, R and H**
23(1)	The Minister may, by notice in the *Gazette* and subject to conditions, give provisional consent to the sale or supply of a new medicine where s/he considers that it is desirable that the medicine be sold, supplied, or used on a restricted basis for the treatment of a limited number of patients.	DG; Chief Medical Officer, Clinical Leadership Protection and Regulation; Group Manager, Medsafe	**DG, R and H**

Section	Summary of function/responsibility/power	Persons Exercising Existing Delegation	Delegation(s) and Sub-Delegation(s) Confirmed or Created
	MEDICINES ACT 1981		
23(3)	On giving his/her provisional consent under this section, the Minister may impose— (a) Such conditions relating to the persons to whom the medicine may be sold or supplied; or (b) Such conditions relating to the area in which the medicine may be distributed; or (c) Such other conditions, not being inconsistent with the purposes of this section,— as s/he thinks fit.	DG; Chief Medical Officer, Clinical Leadership Protection and Regulation; Group Manager, Medsafe	**DG, R and H**
23(4)	Subject to subsections (4A) and (5), every provisional consent given under this section has effect for 2 years or such shorter period as the Minister may determine.	DG; Chief Medical Officer, Clinical Leadership Protection and Regulation; Group Manager, Medsafe	**DG, R and H**
23(4A)	The Minister may, by notice in the *Gazette*, from time to time renew any provisional consent given under this section for a period not exceeding 2 years on any one occasion.	DG; Chief Medical Officer, Clinical Leadership Protection and Regulation; Group Manager, Medsafe	**DG, R and H**
23B	Where the Minister receives, or received not more than 5 years before the commencement date, an innovative medicine application and confidential supporting information, the Minister must take reasonable steps to ensure the confidential supporting information for the innovative medicient applications is kept confidential, and may not use that confidential information for the purposes of any other application.	DG; Chief Medical Officer, Clinical Leadership Protection and Regulation; Group Manager, Medsafe	**DG, R and H**
23C	The Minister may disclose confidential supporting information in any of the circumstances set out in s23C.	DG; Chief Medical Officer, Clinical Leadership Protection and Regulation; Group Manager, Medsafe	**DG, R and H**
24(5)	The Minister must consider distribution of a changed medicine where referral of a changed medicine application has been made by the Director General.	DG; Chief Medical Officer, Clinical Leadership Protection and Regulation; Group Manager, Medsafe; Manager Product Regulation, Medsafe	**DG, R, H, I**

Section	Summary of function/responsibility/power	Persons Exercising Existing Delegation	Delegation(s) and Sub-Delegation(s) Confirmed or Created
	MEDICINES ACT 1981		
24A and 24B	The Minister may consent to the Director General approving the release of a qualifying new medicine under section 38I of the Hazardous Substances and New Organisms Act 1996 (HSNO). If Director General declines approval, Minister must not consent under section 20 or give provisional consent under section 23 for that medicine unless he receives written advice from ERMA that the medicine has been approved for release under HSNO.		

Section	Summary of function/responsibility/power	Persons Exercising Existing Delegation	Delegation(s) and Sub-Delegation(s) Confirmed or Created
	MEDICINES ACT 1981		
24D and 24F	The Minister may receive an application under this section, and may approve with or without conditions, a medicine that is or contains a hazardous substance or new organism, for use in a special emergency, by notification in the *Gazette*, provided that the Minister is satisfied that - (a) the special emergency has been declared and has not come to an end; and (b) the medicine is required for the special emergency; and (c) the application complies with s24D(3). The Minister may specify a date of expiry for the approval.		
29(3)	The Minister may prohibit a person selling or supplying new medicine to medical practitioners before the Minister's consent to distribution formally notified, in circumstances where that person has failed to comply with the requirement in s29(2) to notify such sales or supplies to the Director-General at the end of each month of sale/supply.	DG; Chief Medical Officer, Clinical Leadership Protection and Regulation; Group Manager, Medsafe	DG, R and H
35(1)	The Minister may at any time by notice in the *Gazette*, revoke or suspend for such a period as s/he may determine, any consent given under section 20 (New medicines) or 23 (Provisional consent) if s/he is of the opinion that – (a) The medicine cannot now be regarded as a medicine that can be administered or used safely for purposes indicated in application for consent, or in a section 24 (Distribution of changed medicines restricted) notice; or (b) specifications and standards with respect to the manufacture of that medicine that were included in the terms of a consent cannot now be regarded satisfactory; or (c) the efficacy of the medicine cannot now be regarded as satisfactory.	DG; Chief Medical Officer, Clinical Leadership Protection and Regulation; Group Manager, Medsafe	DG, R and H
36(3)	The Minister may, by notice in writing to the importer or manufacturer in any case where the Director-General or Minister considers an established medicine may be unsafe or ineffective for the therapeutic purpose for which it is sold, prohibit the importer or manufacturer of that medicine from selling or supplying it (either indefinitely or for a specified period); or impose conditions (to be specified in the notice) on the sale or supply of that medicine by the importer or manufacturer.		DG, R and H
36(4)	The Minister may at any time (by a like notice) revoke any notice given under section 36(3) or vary, revoke, or add to any conditions imposed in any such notice.		DG, R and H

Section	Summary of function/responsibility/power	Persons Exercising Existing Delegation	Delegation(s) and Sub-Delegation(s) Confirmed or Created
	MEDICINES ACT 1981		
37(1)	The Minister may from time to time by notice in the *Gazette* prohibit the import, manufacture, packing, sale, possession, supply, administration, or other use of medicines of any specified description or medical devices of any specified kind, whether absolutely or subject to conditions as s/he thinks fit, for any specified period (not exceeding a year). The Minister may not exercise this power more than once in respect of those medicines or medical devices so specified.	DG; Chief Medical Officer, Clinical Leadership Protection and Regulation; Group Manager, Medsafe	**DG, R and H**
37(2)	On the written request of any person, the Minister must state reasons for issuing notice under section 37(1).	DG; Chief Medical Officer, Clinical Leadership Protection and Regulation; Group Manager, Medsafe	**DG, R and H**
48(1) and (2)	The Minister may at any time by notice in the *Gazette* – (a) prohibit any specified practitioner, veterinarian, registered midwife, or designated prescriber from prescribing prescription medicines or any class or description of medicines (b) prohibit (either generally or in relation to any particular class or description of medicines) any specified person from exercising all or any of the rights conferred by the Medicines Act, whether those righs are so conferred on persons generally or on a particular class to which that person belongs. Note that under 48(2), the Minister not use any power conferred on him/her by section 48(1) in relation to the following persons: (a) a medical practitioner (except on the recommendation of the Medical Council) (b) a dentist (except on the recommendation of the Dental Council) (c) a pharmacist (except on the recommendation of the council of the Pharmaceutical Society) (d) One person with wide experience in a form of chemistry other than pharmaceutical chemistry. (e) a veterinarian (except on the recommendation of the Veterinary Council of New Zealand) (f) a designated prescriber (to whom (c) and (d) do not apply) except of the recommendation of the Council or Board, specified in regulations made under the Medicines Act, which has jurisdiction in respect of the class of registered health professional to which the designated prescriber belongs.	DG; Chief Medical Officer, Clinical Leadership Protection and Regulation; Manager, Provider Regulation	**DG, R**
48(3)	Minister from time to time by notice in the *Gazette*, revoke any notice given under section 48(1)	DG; Chief Medical Officer, Clinical Leadership Protection and Regulation; Manager, Provider Regulation	**DG, R**

Section	Summary of function/responsibility/power	Persons Exercising Existing Delegation	Delegation(s) and Sub-Delegation(s) Confirmed or Created
	MEDICINES ACT 1981		
49(5)	a person aggrieved by the issue of a notice section 49 (Restrictions on supply to particular persons) or by the refusal of the Medical Offcer of Health to revoke, vary, or modify any prohibition, condition, or exception contained in any such notice, may appeal in writing to the Minsiter. The Minister's decision will be final.	DG; Chief Medical Officer, Clinical Leadership Protection and Regulation; Group Manager, Medsafe	**DG, R and G**
61(1) (c)	Without limiting section 105 (Regulations) of the Medicines Act but subject to subsection 62(2), the Governor-General may, by Order in Council, make regulations to enable the Minister to require, after consultation with organisations that appear to Minister to represent any classes of persons whose interests might be affected by the requirement, the insertion of particular words specified by Minister in, or omission of particular words or other matter so specified from, any medical advertisement or class of medical advertisement; and to give directions for the location, size, and appearance of the insertion and with respect to other incidental matters, and providing a right of appeal in respect of any such requirement or direction.		
62(2)	Any regulations made by Governor-General under section 66(1)(a) (Requiring and egulating the insertion in any medical advertisement) shall be made only on the recommendation of the Minsiter after consultation with such organisations or bodies the Minister considers likely to be substantially affected by the regulations.	DG; Chief Medical Officer, Clinical Leadership Protection and Regulation; Group Manager, Medsafe	**DG, R and H**
85(2)	Everything forfeited to the Crown by the Court under section 85(1), for conviction of an offence against the Medicines Act or any egulations made under the Medicines Act, shall be disposed of as Minister directs.	DG; Chief Medical Officer, Clinical Leadership Protection and Regulation; Group Manager, Medsafe	**DG, R and H**
91(3)	If High Court or Court of Appeal modifies a decision of Medicines Review Committee, or substitutes a new decisions, the Minister, if the case requires him/her to take staps, will take all necessary steps to implement the Court's decision.	DG; Chief Medical Officer, Clinical Leadership Protection and Regulation; Group Manager, Medsafe	**DG, R and H**
96C	The Minister may, by notice in writing, authorise a person or a body of persons to conduct a particular specified biotechnical procedure, with or without conditions, if s/he is safisfied that the conduct of the procedure meets criteria specified in section 96E(1). A notice can be varied or revoked by the Minister, or made subject to new conditons. As soon as practicable after a notice issued, varied or revokved, Minister must publish the notice in the *Gazette* and present to the house.		
96E	The Minister may only grant authorisation for an application sought under section 96G, if specified biotechnical procedure meets the following criteria: (a) the conduct of the procedure or class of procedure does not pose an unacceptable risk to the health or		

Section	Summary of function/responsibility/power	Persons Exercising Existing Delegation	Delegation(s) and Sub-Delegation(s) Confirmed or Created
	MEDICINES ACT 1981		
	(b) any risks posed by the conduct of the procedure or class of procedure will be appropriately managed; (c) any ethical issues have been adequately addressed; (d) any cultural issues have been adequately address; (e) any spiritual issues have been adequately addressed. If the Minister is not satisfied that the conduct of the procedure or class of procedure to which the application relates meets any 1 or more of the criteria specified in subsection (1), the Minister - (a) may direct that advice on the question whether or not the conduct of the procedure or class of procedure meets that criterion (or, as the case may be, those criteria) be obtained from persons who, in the Minister's opinion, are appropriately qualified, or have the appropriate expertise, to advise on the question; and (b) after obtaining that advice, may resume his or her consideration of the application on the basis of that advice.		
96F(1)	For the purpose of obtaining advice of the kind referred to in section 96E(3)(a) in relation to an application, the Minister may do any 1 or more of the following: (a) establish a committee to advise on the criteria in question; (b) request a body or a committee or an association of persons formed or recognised by or under an enactment to advise on the criteria in question; (c) request the person who made the application under section 96G (in this section referred to as the applicant) to obtain advice on the criteria in question from a committee consisting of persons nominated by the Minister.		
96F(4)	The Minister may agree with an applicant whose application relates to the work of a committee, body, or association established or requested under (a) or (b) above, that the applicant will pay, or contribute towards the payment of, any costs incurred or to be incurred by the committee or body or association in the examination of aspects of the applicant's application that, in the Minister's opinion, could have significant commercial benefits (whether or not that examination also benefits the public).		
96F(5)	The Minister may agree with an applicant whose application relates to the work of a committee of persons nominated by the Minister under (c) above that the Minister will pay, or contribute towards the payment of, any costs incurred or to be incurred by the committee in the examination of aspects of the applicant's application that, in the Minister's opinion, are likely to benefit the public (whether or not that examination also has commercial benefits.		
96F(6)	If the Minister is attempting to reach an agreement with the applicant, the Minister may direct the committee, body, or association concerned not to consider any matters relating to the applicant's application until agreement under subsection (4) has been reached; and the committee or body or association must give effect to that direction.		
96G	The Minister may receive applications to grant authorisation for biotechnical procedures under section 96C, or to recommend authorisation under section 96D(1). The Minister may defer consideration of the application if he has requested the applicant to obtain advice under section 96F(1)(c), until the applicant has received that advice.		

Section	Summary of function/responsibility/power	Persons Exercising Existing Delegation	Delegation(s) and Sub-Delegation(s) Confirmed or Created
	MEDICINES ACT 1981		
96J	The Minister may recommend that the Governor General specify a date later than 31 December 2008 for the expiry of Part 7A of the Medicines Act (Restrictions on specified biotechnical procedures).		
105(1)	The Governor-General may, by Order in Council made on the advice of Minister tendered after consultation with such organisations or bodies as appear to Minister to be representative of persons likely to be substantially affected by the regulations, make regulations for all or any of the purposes listed in section 105(1).		
105A	For the purpose of regulations under this section the Minister may from time to time by notice in the *Gazette* specify qualifications that must be obtained by a practitioner, midwife or veterinarian, or any training that must be undertaken by such groups.		**DG, R**
105B	Similar provision to s105A in relation to designated prescribers.		**DG, R**
105C	(1) The Governor-General may, by Order in Council made on the recommendation of the Minister, - (a) exempt any person or class of person from any of the requirements of section 55D(2)(a) or section 55E(1)(a) (relating to pharmacy ownership and operation); (b) modify the application of theprovisions of section 55D(2)(a) or section 55E(1)(a) in respect of any person or class of person. (2) The Minister must not recommend the making of any Order in Council under subsection (1) unless in the opinion of the Minister - (a) health services or access to those services will be improved by the making of that Order in Council; and (b) the making of that Order in Council is necessto meet the needs of the community in the particular location of the pharmacy or proposed pharmacy. (3) The Minister's reasons for making the recommendation must be included in, or appended to, the Order in Council.		
106(1)	The minister may by notice in the *Gazette* declare any medicine to be a prescription medicine or a restricted or pharmacy-only medicine.	DG; Chief Medical Officer, Clinical Leadership Protection and Regulation; Group Manager, Medsafe	**DG, R and H**
106(3)	The Minister may revoke a notice issued under s106(1) earlier than its expiry date (six months after issue).	DG; Chief Medical Officer, Clinical Leadership Protection and Regulation; Group Manager, Medsafe	**DG, R and H**

DELEGATION OF POWERS BY THE

DIRECTOR-GENERAL OF HEALTH

under section 41 of the State Sector Act 1988

The powers and functions of the Minister of Health under the statutes and regulations administered by the Ministry of Health, are delegated by the Minister of Health under section 28 of the State Sector Act 1988 by instrument dated 11 September 2013.

The column of the table in Appendix One headed "Delegations confirmed or created" lists the powers and functions delegated by the Minister of Health. As well as powers delegated to the Director-General of Health, it lists the persons to whom those powers shall be sub-delegated by the Director-General of Health.

I delegate to the classes of office holders the Ministerial powers and functions as listed in column of the table in Appendix One of that instrument headed "Delegations confirmed or created".

The delegation of a power to a class of office holder shall include delegation of that power to a person validly acting in that class.

All previous delegations of the Director-General of Health of Ministerial powers relating to the powers and functions set out in the Ministerial delegation dated September 2013 are hereby revoked,

The powers hereby delegated by me remain subject to my general control.

These delegations are made on 20 September 2013 under section 41 of the State Sector Act 1988.

Kevin Woods
Director-General of Health

Regulatory Affairs Department Australia/New Zealand
Pfizer Australia
Level 15-18, 151 Clarence Street
Sydney NSW 2000
Australia

21 October 2020

The Manager
MEDSAFE
Ministry of Health
133 Molesworth Street
Thorndon Wellington 6011
NEW ZEALAND

Dear Sir/Madam,

Re: **New Medicine Application**
COVID-19 Vaccine (BNT162b2 [mRNA]) concentrated suspension for injection, 30 µg/0.3 mL, 0.45 mL multi-dose vial

This application seeks provisional registration of a new biological entity, BNT162b2 [mRNA], hereafter referred to as BNT162b2, under section 23 of the Medicines Act, for an RNA-based vaccine to prevent Coronavirus Disease 2019 (COVID-19) caused by the SARS-CoV-2 virus.

Pfizer and BioNTech have partnered to develop a nucleoside-modified messenger RNA encoding the SARS-CoV-2 S-glycoprotein intended to provide immunisation against COVID-19 caused by the virus, SARS-CoV-2. The vaccine is formulated as a preservative-free concentrated suspension formulation. Given that the available options for approved dosage terminology (injection, concentrate and injection, suspension) inadequately describe the proposed vaccine, Pfizer seeks to use 'concentrated suspension for injection' as the dosage form description. The vaccine will be supplied in multi-dose glass vials containing 0.45 mL vaccine concentrate, which requires dilution with 1.8 mL 0.9% saline. The diluted suspension is sufficient to administer five 0.3 mL injections. Vaccination requires two intra-muscular injections given 21 days apart.

Proposed Indication

Active immunisation against COVID-19 disease caused by SARS-CoV-2 virus in individuals aged 16 years and over.

Disease Background

Since late 2019, COVID-19 has reached pandemic levels, with over 38 million cases and over 1 million deaths as of 15 October 2020, according to the World Health Organization (https://covid19.who.int/). Case numbers and mortality are continuing to rise globally. There are

currently no available vaccines to protect against SARS-CoV-2 infections or the disease it causes, COVID-19.

Presubmission Meeting

A pre-submission meeting was held with Medsafe on 24 September 2020 to discuss the proposed application to register this SARS-CoV-2 vaccine. Given the global COVID-19 pandemic that remains a threat to New Zealand as well as all other countries, the development of the proposed vaccine has been expedited to facilitate the earliest possible regulatory filing and registration. Consequently, some data normally required at the time of initial dossier submission will not be available until a later date. In the interest of public health, Medsafe and Pfizer have come to an agreement regarding the requirements for this registration application, as confirmed in the minutes for the pre-submission meeting. This application is seeking provisional consent of the COVID-19 Vaccine (BNT162b2 [mRNA]) and is being filed as a rolling submission. s 9(2)(b)(ii), s 9(2)(ba)(i)

Pharmacology Background

The Pfizer and BioNTech COVID-19 Vaccine is based on SARS-CoV-2 spike (S) glycoprotein antigens encoded in RNA and formulated in lipid nanoparticles (LNPs), referred to as COVID-19 Vaccine (BioNTech code number BNT162b2, Pfizer code number PF-07302048).

The RNA-based vaccine encodes a viral antigen which is expressed by the vaccine recipient and can elicit protective immune responses. Unlike live attenuated vaccines, RNA vaccines do not carry risks associated with infection. RNA-based vaccines are manufactured by a cell-free *in vitro* transcription process, which allows easy and rapid production and the prospect of producing high numbers of vaccine doses within a shorter time period than could be traditionally achieved with conventional vaccine approaches.

Several variants of the BNT162 vaccine were used in the non-clinical and Phase 1 clinical studies before the decision was made to progress with the variant designated as BNT162b2. The variants, which are characterised in these studies, are summarised below:

BNT162 vaccine candidate	RNA platform	Encoded antigen
s 9(2)(b)(ii)		
BNT162b2	Nucleoside Modified mRNA	Full length SARS-CoV-2 spike protein bearing mutations preserving neutralisation-sensitive sites
s 9(2)(b)(ii)		

After reviewing the Phase 1 safety and immunogenicity data, the active ingredient selected to progress through to the Phase 2/3 of the pivotal clinical study (*C4591001*) was BNT162b2 [mRNA], which utilises a nucleoside-modified mRNA (modRNA) platform. The vaccine was shown to express a prefusion stabilised full-length variant of the SARS-CoV-2 S-glycoprotein.

BNT162b2-vaccinated human participants displayed a favourable breadth of epitopes recognised in T cell responses specific to the SARS-CoV-2 spike antigen. In addition, BNT162b2 demonstrated concurrent induction of high magnitude CD4+ and CD8+ T cell responses against the receptor binding domain (RBD) and against the remainder of the spike glycoprotein.

Non-clinical Data

This initial submission includes a full non-clinical data package, as discussed at the pre-submission meeting with Medsafe.

To enable the rapid development of prophylactic vaccines during public health emergencies, as is the case for the current SARS-CoV-2 outbreak, the WHO has published recommendations on the

content of a non-clinical safety package to support initiation of clinical testing. This guideline is considered applicable for this BNT162b2 vaccine, due to the pandemic situation.

The primary pharmacology of several BNT162 vaccine candidates was evaluated in a range of non-clinical pharmacology studies *in vitro* and *in vivo*. They were all found to be immunogenic in non-clinical models including mice, rats, and non-human primates (NHPs), resulting in inducing robust immune responses. The toxicology of BNT162 vaccine candidates was studied in a GLP-compliant, repeat-dose study.

None of the components of the BNT162 vaccines (lipids and RNA) are suspected to have genotoxic potential. In addition, no impurity or component of the delivery system warrants genotoxicity testing. Therefore, in accordance with the WHO guideline, no genotoxicity studies were performed.

RNA itself, and the lipids used in the BNT162 vaccines, have no carcinogenic or tumorigenic potential. Furthermore, according to ICH S1A, no carcinogenicity studies are required for therapeutics that are not continuously administered. Therefore, no carcinogenicity studies were performed.

Macroscopic and microscopic evaluation of male and female reproductive tissues were included in the GLP repeat-dose toxicity study testing of BNT162b2 in rat. No changes in these tissues were reported. Specific fertility and embryofetal development studies are ongoing.

No dedicated immunotoxicity study was conducted, however immunotoxicity of BNT162b2 was assessed in repeated-dose toxicity study in rats. No vaccine-related systemic intolerance or mortality was observed in these studies.

Clinical Data

Phase 1 Studies

First-in-human dose-ranging studies were conducted in a Phase 1/2 study (BNT162-01) in Germany in which all 15 participants were 18-85 years of age and received active vaccine. The study purpose was to gather safety and immunogenicity data for the different dose levels used. The study found the 30 µg dose to be the optimal dose to progress into phase 2/3 of the pivotal study.

Phase 1 data from the German study BNT162-01 (1, 3, 10, 20, 30 µg) and also Study C4591001 (10, 20, 30 µg) showed that across all populations, BNT162b2 administration was well tolerated with mild to moderate fever in fewer than 20% of the participants.

Pivotal Studies

The Phase 2/3 part of study C4591001 involved randomisation of participants in a 1:1 ratio with placebo. It commenced on 27 July 2020 and is designed to evaluate the safety, efficacy and immunogenicity of BNT162b2 in over 30,000 participants aged ≥18 years of age. To date, more than 35,000 participants have been en rolled, including from areas with significant SARS-CoV-2 transmission. In the USA, the sponsor is currently in discussion with the FDA to reduce the minimum age for participants to be eligible for C4591001 Phase 3 from 18 years to 12 years.

Pfizer will submit an initial dossier based on interim analysis of Study C4591001, in which efficacy is demonstrated, and will submit the final analysis of efficacy, in addition to safety data, when

available, as agreed with Medsafe. Study C4591001 includes four planned interim analyses (to be conducted at accrual of 32, 62, 92, and 120 confirmed COVID-19 cases) and targets 164 cases in total at the final analysis. Based on anticipated enrolment rates and disease incidence of 0.9% per month in the placebo group, demonstration of the primary and key secondary study endpoints for safety and efficacy is anticipated by early November 2020.

Quality Data

No Module 3 (Quality) data are included with this initial filing, however as agreed, data will be submitted once available, as part of this provisional consent application.

International Regulatory Status

Applications for this vaccine are currently under review in Europe, Canada and Switzerland, and is currently pending submission in Australia. The US filing is planned for January 2021.

CTD Dossier and Content

In support of this application, a dossier is provided in eCTD format via Medsafe's electronic file transfer (EFT) system. Payment of the evaluation fee for this application will be made via electronic funds transfer upon receipt of the invoice from Medsafe.

Pfizer looks forward to Medsafe's earliest review of the enclosed application. Should you require clarification or have any questions regarding the above information, please do not hesitate to contact the undersigned.

Yours faithfully,

s 9(2)(a)

Senior Regulatory Affairs Associate

Ph: s 9(2)(a)
Email: s 9(2)(a)
RegulatoryAffairs.ANZ@Pfizer.com

Terms of Reference
Medsafe COVID-19 Vaccine Advisory Group

1. Introduction

1.1 These Terms of Reference establish the Medsafe COVID-19 Vaccine Advisory Group (the Group) and set out the:

- role and functions of the Group
- composition of the Group
- term and workplan requirements
- reporting requirements
- terms and conditions of appointment
- duties and responsibilities of Group members.

2. Functions of the Group

2.1 The purpose and function of the Medsafe COVID-19 Vaccine Advisory Group is to provide expert advice in-confidence to Medsafe. The Group does not have powers of veto, direction, or instruction actual or implied.

2.2 The Group is to be a pool of experts convened to provide advice on specific questions raised by Medsafe. These questions will be identified during the Medsafe evaluation of applications by sponsors for approval to market Covid-19 vaccines. The information will assist Medsafe in determining if such applications can be granted consent under the Medicines Act 1981.

3. Composition of the Group

3.1 The membership of the Group will consist of a pool of experts in aspects of vaccine manufacture, quality, safety and efficacy. There will be a Chair to allocate the questions to the experts and sign the resulting reports.

3.2 The term of the membership of the Group will be determined by Medsafe.

3.3 In making themselves available for appointment, members should ensure that:

- there is no conflict of interest which would preclude their appointment; and
- they are available to serve for the full term of their appointment.

4. Workplan Development

4.1 The Group will not be asked to develop a workplan. Questions to the Group will be commissioned by Medsafe.

5. Reporting Requirements

5.1 When ad hoc meetings of the Group are held, summaries will be produced by the secretary but not published. Summaries are subject to the Official Information Act 1982 (OIA) but any confidential information will be withheld.

5.2 The commissioning templates will include a section for reports detailing the expert advice provided in response to the question(s) and are to be written. These completed templates will be provided to Medsafe following consideration by the member(s) of the Group. These reports will be stored alongside the Medsafe assessment reports but will not be provided with the assessment reports to sponsors. Templates with the responses are subject to the OIA as per above

5.3 Information on the number of questions and time taken to reply will be reported to the Group Manager, Medsafe on a monthly basis.

5.4 A report to the Health System Improvement and Innovation Deputy Director-General and the appropriate COVID vaccine governance group will be provided at the Group's end date.

6. Establishment, Review Process and End Date

6.1 The Group will be established by the Group Manager, Medsafe for the purposes of providing technical advice on the evaluation of COVID-19 vaccines for approval.

6.2 The Group's Terms of Reference will be reviewed at 12 monthly intervals alongside the Ministry's annual stocktake of Ministerial and Ministry Groups.

7. Meetings

7.1 It is intended that the Group will do most of its work virtually via email and teleconferencing. It is not intended that all Group members be present at meetings to provide advice. If necessary, meetings will be held on an ad hoc basis. Meetings may be held face-to-face if necessary and appropriate.

7.2 A Commissioning template will be used for the questions from Medsafe to the Group. This template will include a summary of information relevant to the questions. Any relevant data from the new medicine application will be provided as attachments to the template. The information will be transmitted and accessed via a secure electronic file transfer system (EFT).

7.3 Commissioning templates will be sent to the Chair for allocation to individual members with expertise most relevant to the question(s) posed. Allocation will be via the EFT. The member(s) will write a report detailing their advice, which will go through peer review and Chair sign-off before being returned to Medsafe via the EFT.

7.4 Completed reports must be returned to Medsafe within the requested number of working days of the Group receiving the request for advice. The reference timeframe is 10 working days from receipt unless determined by the Chair and/or Medsafe that this is not feasible.

7.5 The Secretariat supporting the Group will maintain an interests register, listing members' interests relevant to the Group's business.

8. Duties and Responsibilities of a Member

8.1 Members have a commitment to work for the public of New Zealand. Members are accountable to the Ministry of Health.

8.2 Group members attend meetings and undertake Group activities as independent persons responsible to the Group as a whole and are not representatives of professional organisations or communities. This issue is particularly important when Group members may, at times, be required to be party to decisions which conflict with the views of other organisations with which they are involved.

8.3 There is an expectation that members will attend all meetings and devote sufficient time to become familiar with the affairs of the Group and the wider environment within which it operates.

8.4 Members of the group are asked to:

- Provide an honest expert opinion on questions raised by Medsafe
- Provide advice on resolving any identified issues
- Identify any potential conflicts of interest
- Maintain confidentiality of the data provided
- Adhere to the timelines stated in the Commissioning template in order to facilitate the timely review of COVID-19 vaccine new medicine applications by Medsafe.

9. Removal from Group

9.1 The Ministry may, at any time and entirely at the Ministry's discretion, remove any member from the Group.

9.2 The Ministry may, at any time, exclude a member from discussions of the Group in the case of a conflict of interest.

10. Conflicts of Interest

10.1 Members should perform their functions in good faith, honestly and impartially and avoid situations that might compromise their integrity or otherwise lead to conflicts of interest. Proper observation of these principles will enable public confidence in the work of the Group to be maintained.

10.2 When members believe they have a conflict of interest on a subject which will prevent them from reaching an impartial decision or undertaking an activity consistent with the Group's functions, then they must declare a conflict of interest. The conflict can be determined by the Group, and measures can be determined by the Group in cases where the conflict is unclear. Members with a conflict of interest must absent themselves from the discussion and/or activity. This must be done at the earliest possible opportunity, in the regular agenda item around conflicts of interest, and at the point the relevant item of business comes up in the meeting.

11. Liability

11.1 Members are not liable for any act or omission done or omitted in their capacity as a member, if they acted in good faith, and with reasonable care, in pursuance of the functions of the Group.

12. Confidentiality

12.1 Meetings, including agenda material and minutes, are confidential. Members must ensure that the confidentiality of Group business is maintained.

12.2 Members are free to, and are expected to, express their own views within the context of meetings, or the general business of the Group. Members must publicly support a course of action decided by the Group, or if unable to do that, must not publicly comment on decisions.

12.3 At no time shall members divulge details of Group matters or decisions to people who are not members, or Ministry employees. Disclosure of Group business to anyone outside the Ministry must be the decision of the Ministry.

12.4 Group members must ensure that documents are kept securely to ensure that confidentiality is maintained. Release of correspondence or papers can only be made with the approval of the Ministry in writing. At the end of a member's term, all Group information must be returned to the Ministry.

13. Remuneration and expenses

13.1 Members of the Group are paid fees for attendance at meetings, in accordance with the Cabinet Office Circular CO (12) 6 *Fees framework for members appointed to bodies in which the Crown has an interest* (or its successor circular).

13.2 The fee for Group members is currently $395 per day and $50 per hour for any part day (before tax) and this is reviewed annually.

13.3 Members who are employees of the wider State sector are not entitled to be paid fees for Group business if this is conducted during regular paid work time (ie, members cannot be paid twice by the Crown for the same hours).

13.4 Members are entitled to be reimbursed for actual and reasonable travelling and other expenses incurred in carrying out their duties. The expectation is that the standards of travel, accommodation, meals and other expenses are modest and appropriate to reflect public sector norms.

Clare Perry
Acting Deputy Director-General
Health System Improvement and Innovation

Approved on: 4 November 2020

Date for next review: 29 October 2021

Regulatory Affairs Department Australia/New Zealand
Pfizer Australia
Level 15-18, 151 Clarence Street
Sydney NSW 2000
Australia

21 October 2020

The Manager
MEDSAFE
Ministry of Health
133 Molesworth Street
Thorndon Wellington 6011
NEW ZEALAND

Dear Sir/Madam,

Re: **New Medicine Application**
COVID-19 Vaccine (BNT162b2 [mRNA]) concentrated suspension for injection, 30 µg/0.3 mL, 0.45 mL multi-dose vial

This application seeks consent of a new biological entity, BNT162b2 [mRNA], hereafter referred to as BNT162b2, for an RNA-based vaccine to prevent Coronavirus Disease 2019 (COVID-19) caused by the SARS-CoV-2 virus.

Pfizer and BioNTech have partnered to develop a nucleoside-modified messenger RNA encoding the SARS-CoV-2 S-glycoprotein intended to provide immunisation against COVID-19 caused by the virus, SARS-CoV-2. The vaccine is formulated as a preservative-free concentrated suspension formulation. Given that the available options for approved dosage terminology (injection, concentrate and injection, suspension) inadequately describe the proposed vaccine, Pfizer seeks to use 'concentrated suspension for injection' as the dosage form description. The vaccine will be supplied in multi-dose glass vials containing 0.45 mL vaccine concentrate, which requires dilution with 1.8 mL 0.9% saline. The diluted suspension is sufficient to administer five 0.3 mL injections. Vaccination requires two intra-muscular injections given 21 days apart.

Proposed Indication

Active immunisation against COVID-19 disease caused by SARS-CoV-2 virus in individuals aged 16 years and over.

Disease Background

Since late 2019, COVID-19 has reached pandemic levels, with over 39 million cases and over 1.1 million deaths as of 19 October 2020, according to the World Health Organization (https://covid19.who.int/). Case numbers and mortality are continuing to rise globally. There are

currently no available vaccines to protect against SARS-CoV-2 infections or the disease it causes, COVID-19.

Presubmission Meeting

A pre-submission meeting was held with Medsafe on 24 September 2020 to discuss the proposed application to register this SARS-CoV-2 vaccine. Given the global COVID-19 pandemic that remains a threat to New Zealand as well as all other countries, the development of the proposed vaccine has been expedited to facilitate the earliest possible regulatory filing and registration. Consequently, some data normally required at the time of initial dossier submission will not be available until a later date. In the interest of public health, Medsafe and Pfizer have come to an agreement regarding the requirements for this registration application, as confirmed in the minutes for the pre-submission meeting. This application is seeking provisional consent of the COVID-19 Vaccine (BNT162b2 [mRNA]) and is being filed as a rolling submission. s 9(2)(b)(ii), s 9(2)(ba)(i)

Pharmacology Background

The Pfizer and BioNTech COVID-19 Vaccine is based on SARS-CoV-2 spike (S) glycoprotein antigens encoded in RNA and formulated in lipid nanoparticles (LNPs), referred to as COVID-19 Vaccine (BioNTech code number BNT162b2, Pfizer code number PF-07302048).

The RNA-based vaccine encodes a viral antigen which is expressed by the vaccine recipient and can elicit protective immune responses. Unlike live attenuated vaccines, RNA vaccines do not carry risks associated with infection. RNA-based vaccines are manufactured by a cell-free *in vitro* transcription process, which allows easy and rapid production and the prospect of producing high numbers of vaccine doses within a shorter time period than could be traditionally achieved with conventional vaccine approaches.

Several variants of the BNT162 vaccine were used in the non-clinical and Phase 1 clinical studies before the decision was made to progress with the variant designated as BNT162b2. The variants, which are characterised in these studies, are summarised below:

BNT162 vaccine candidate	RNA platform	Encoded antigen
s 9(2)(b)(ii) [redacted]		
BNT162b2	Nucleoside Modified mRNA	Full length SARS-CoV-2 spike protein bearing mutations preserving neutralisation-sensitive sites
s 9(2)(b)(ii) [redacted]		

After reviewing the Phase 1 safety and immunogenicity data, the active ingredient selected to progress through to the Phase 2/3 of the pivotal clinical study (*C4591001*) was BNT162b2 [mRNA], which utilises a nucleoside-modified mRNA (modRNA) platform. The vaccine was shown to express a prefusion stabilised full-length variant of the SARS-CoV-2 S-glycoprotein.

BNT162b2-vaccinated human participants displayed a favourable breadth of epitopes recognised in T cell responses specific to the SARS-CoV-2 spike antigen. In addition, BNT162b2 demonstrated concurrent induction of high magnitude CD4+ and CD8+ T cell responses against the receptor binding domain (RBD) and against the remainder of the spike glycoprotein.

Non-clinical Data

This initial submission includes a full non-clinical data package, as discussed at the pre-submission meeting with Medsafe.

To enable the rapid development of prophylactic vaccines during public health emergencies, as is the case for the current SARS-CoV-2 outbreak, the WHO has published recommendations on the

content of a non-clinical safety package to support initiation of clinical testing. This guideline is considered applicable for this BNT162b2 vaccine, due to the pandemic situation.

The primary pharmacology of several BNT162 vaccine candidates was evaluated in a range of non-clinical pharmacology studies *in vitro* and *in vivo*. They were all found to be immunogenic in non-clinical models including mice, rats, and non-human primates (NHPs), resulting in inducing robust immune responses. The toxicology of BNT162 vaccine candidates was studied in a GLP-compliant, repeat-dose study.

None of the components of the BNT162 vaccines (lipids and RNA) are suspected to have genotoxic potential. In addition, no impurity or component of the delivery system warrants genotoxicity testing. Therefore, in accordance with the WHO guideline, no genotoxicity studies were performed.

RNA itself, and the lipids used in the BNT162 vaccines, have no carcinogenic or tumorigenic potential. Furthermore, according to ICH S1A, no carcinogenicity studies are required for therapeutics that are not continuously administered. Therefore, no carcinogenicity studies were performed.

Macroscopic and microscopic evaluation of male and female reproductive tissues were included in the GLP repeat-dose toxicity study testing of BNT162b2 in rat. No changes in these tissues were reported. Specific fertility and embryofetal development studies are ongoing.

No dedicated immunotoxicity study was conducted, however immunotoxicity of BNT162b2 was assessed in repeated-dose toxicity study in rats. No vaccine-related systemic intolerance or mortality was observed in these studies.

Clinical Data

Phase 1 Studies

First-in-human dose-ranging studies were conducted in a Phase 1/2 study (BNT162-01) in Germany in which all 15 participants were 18-85 years of age and received active vaccine. The study purpose was to gather safety and immunogenicity data for the different dose levels used. The study found the 30 µg dose to be the optimal dose to progress into phase 2/3 of the pivotal study.

Phase 1 data from the German study BNT162-01 (1, 3, 10, 20, 30 µg) and also Study C4591001 (10, 20, 30 µg) showed that across all populations, BNT162b2 administration was well tolerated with mild to moderate fever in fewer than 20% of the participants.

Pivotal Studies

The Phase 2/3 part of study C4591001 involved randomisation of participants in a 1:1 ratio with placebo. It commenced on 27 July 2020 and is designed to evaluate the safety, efficacy and immunogenicity of BNT162b2 in over 30,000 participants aged ≥18 years of age. To date, more than 35,000 participants have been enrolled, including from areas with significant SARS-CoV-2 transmission. In the USA, the sponsor is currently in discussion with the FDA to reduce the minimum age for participants to be eligible for C4591001 Phase 3 from 18 years to 12 years.

Pfizer will submit an initial dossier based on interim analysis of Study C4591001, in which efficacy is demonstrated, and will submit the final analysis of efficacy, in addition to safety data, when

available, as agreed with Medsafe. Study C4591001 includes four planned interim analyses (to be conducted at accrual of 32, 62, 92, and 120 confirmed COVID-19 cases) and targets 164 cases in total at the final analysis. Based on anticipated enrolment rates and disease incidence of 0.9% per month in the placebo group, demonstration of the primary and key secondary study endpoints for safety and efficacy is anticipated by early November 2020.

Quality Data

No Module 3 (Quality) data are included with this initial filing, however as agreed, data will be submitted once available, as part of this provisional consent application.

International Regulatory Status

Applications for this vaccine are currently under review in Europe, Canada and Switzerland, and is currently pending submission in Australia. The US filing is planned for January 2021.

CTD Dossier and Content

In support of this application, a dossier is provided in eCTD format via Medsafe's electronic file transfer (EFT) system. Payment of the evaluation fee for this application will be made via electronic funds transfer upon receipt of the invoice from Medsafe.

Pfizer looks forward to Medsafe's earliest review of the enclosed application. Should you require clarification or have any questions regarding the above information, please do not hesitate to contact the undersigned.

Yours faithfully,

s 9(2)(a)

Senior Regulatory Affairs Associate

Ph: s 9(2)(a)
Email: s 9(2)(a)
RegulatoryAffairs.ANZ@Pfizer.com

EVALUATION OF A NEW MEDICINE APPLICATION

Product Details	
Type of application:	Higher-risk medicine - Vaccine *This vaccine contains a new biological entity, so a data protection period will apply for 5 years from the date of gazette.*
Proposed trade name:	**COMIRNATY** COVID-19 mRNA vaccine (nucleoside modified)
Dose form:	Concentrated suspension for injection *Approved in the EU as 'concentrate for dispersion for injection'*
Drug substance and strength:	BNT162b2 [mRNA], 0.5 mg/mL (as 225 µg/0.45 mL) Each 0.3 mL dose of the diluted vaccine delivers 30 µg of RNA embedded in lipid nanoparticles. BNT162b2 [mRNA] is single-stranded, 5'-capped messenger RNA produced using a cell-free *in vitro* transcription from the corresponding DNA templates encoding the viral spike (S) protein of SARS-CoV-2. *The term 'tozinameran' has been proposed as an INN for the BNT162b2 drug substance and is currently under consideration by the World Health Organization (WHO).*
Classification:	Prescription
ATC code:	J07BX
Proposed indications and /or label claims	Comirnaty is indicated for active immunisation to prevent ~~against~~ coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals ~~aged~~ 16 years of age and older ~~over~~. The use of this vaccine should be in accordance with official recommendations. *Indication wording revised to align with EU in roll 2*.
Administration & dosage:	*Administration:* Intramuscular injection. The multidose vial containing 0.45 mL of vaccine concentrate requires dilution with 1.8 mL 0.9% saline (not supplied with product) prior to use. Once diluted, the vial can deliver 6 doses ~~5 doses~~ of 0.3 mL. The multi-dose vial is preservative-free. *The number of doses that can be extracted from a single vial was updated by the company on 27/01/2021. The data*

	provided to support this change is discussed in the applicable sections of this report. *Dosage:* Adults and adolescents 16 years of age and older: Two doses of 0.3 mL given at least 21 days apart. Children under the age of 16: Safety and efficacy have not been established in children under 16 years of age.
Packaging & closure:	2 mL clear, glass (Type I) vial, closed with a bromobutyl rubber stopper, aluminium overseal and flip-off cap. The vials are enclosed in a cardboard carton.
Pack size:	195 multidose vials (1170 doses ~~975 doses~~) Each vial contains 0.45 mL of vaccine concentrate.
Storage conditions:	Unopened vials 6 months from the date of manufacture, stored in the freezer at -90°C to -60°C. Protect from light. Once removed from the freezer, the unopened vials can be stored for up to 5 days at 2 to 8°C, and up to 2 hours at temperatures up to 30°C, prior to use. Once thawed, the vaccine should not be refrozen. Diluted vials After dilution, the vials can be stored at 2 to 30°C for up to 6 hours. The data sheet notes that from a microbiological point of view (since there is no preservative), the product should be used immediately.
NZ sponsor:	Pfizer New Zealand Limited, Level 1, Suite 1.4, Building B, 8 Nugent Street, Grafton, AUCKLAND 1023
Manufacturers & packers:	Manufacture and testing of drug substance: Wyeth Biopharma Division of Wyeth Pharmaceuticals LLC, 1 Burtt Road, Andover, Massachussetts 01810, USA *Responsible for manufacture of drug substance, release and stability testing (composition, strength, identity, purity, process-related impurities, safety), and storage of cell banks.* BioNTech Manufacturing GmbH, An der Goldgrube 12, Mainz 55131, GERMANY *Responsible for manufacture of drug substance (in-vitro transcription, DNase I and Proteinase K digestion), release and stability testing (identity, purity, process-related impurities).* Rentschler Biopharma SE, Erwin-Rentschler-Strasse 21, Laupheim 88471, GERMANY *Responsible for manufacture of drug substance (ultrafiltration/diafiltration (UF/DF), dispensing), release and stability testing (composition, strength, safety).* BioNTech Innovative Manufacturing Services GmbH, Vollmersbachstrasse 66, Idar-Oberstein 55743, GERMANY

	Responsible for release and stability testing only (product-related impurities, purity). Not recorded on TPDR. Pfizer Inc, 875 Chesterfield Parkway West, Chesterfield, MO 63017-1732, USA *Responsible for release and stability testing of the drug substance (composition, strength, identity, purity, process-related impurities). The site also performs cell bank manufacture and storage, and manufacture and testing of the starting material (linear DNA template). Not recorded on TPDR.* <u>Manufacture, packaging and testing of drug product:</u> Pfizer Manufacturing Belgium NV, Rijksweg 12, Puurs B-2870, BELGIUM *Responsible for LNP fabrication and bulk drug product formulation, fill and finish, packaging (primary and secondary), release and stability testing (composition, adventitious agents), batch release by qualified person in European Economic Area (EEA)).* The NMA form also refers to i) Pharmacia & Upjohn Company LLC, 7000 Portage Road, Michigan, USA, for manufacture, testing (endotoxin and sterility) and packaging of the drug product, ii) BioNTech Manufacturing GmbH, An der Goldgrube 12, Mainz 55131, Germany for batch release of the drug product, and iii) Pfizer Pharma GmbH Betriebsstatte Karlsruhe, An der Tagweide 5, Karlsruhe 76139, Germany for drug product storage. These sites are not described in section 3.2.P.3.1. In direct discussions with the sponsor it was confirmed that these sites are not proposed for inclusion with the NMA. <u>Finished product testing:</u> Pfizer Ireland Pharmaceuticals, Grange Castle Business Park, Clondalkin, Dublin 22, IRELAND *Responsible for release and stability testing (identity, composition).* Wyeth Biopharma Division of Wyeth Pharmaceuticals LLC, 1 Burtt Road, Andover, Massachussetts 01810, USA *Responsible for release and stability testing (composition and strength, identity, potency, purity, adventitious agents).* Pfizer Inc, 875 Chesterfield Parkway West, Chesterfield, MO 63017-1732, USA *Responsible for release and stability testing (composition and strength, identity, potency, purity, adventitious agents).* Hospira Zagreb Ltd, Prudnicka cesta 60, Prigorje Brdovecko 10291, CROATIA *Responsible for release testing (sterility).* *Hospira is a wholly owned subsidiary of Pfizer Inc.* SGS Lab Simon SA, Vieux Chemin du Poete 10, Wavre B-1301, BELGIUM *Responsible for release testing (sterility).*

	The Hospira and SGS Lab Simon SA sites were not described in the NMA form but were confirmed to be relevant to the New Zealand application in pre-submission discussions with the sponsor. Both the Hospira and SGS Lab Simon sites have also been listed as sterility testing sites in section 3.2.P.3.1 of the CTD, and so have been considered as part of this application. BioNTech Manufacturing GmbH, Kupferbergterrasse 17-19, Mainz 55116, GERMANY *Responsible for batch release by Qualified Person in EEA. Not recorded on TPDR, as the New Zealand site of batch release performs this activity for product released to the New Zealand market.* <u>New Zealand site of batch release:</u> Pfizer New Zealand Limited, Level 1, Suite 1-4, Building B, 8 Nugent Street, Grafton, Auckland 1023
Overseas approvals:	Approved in the EU via the centralised procedure on 21/12/2020 and in Canada on 9/12/2020. The vaccine has also been granted authorisation for temporary/emergency supply in the UK and USA. The vaccine is currently under review in Australia, Switzerland and several other countries throughout the world.
Overseas evaluation reports provided:	None provided with the initial submission, but the EMA questions and final overview report were provided in subsequent data rolls.

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Administrative Data

Background

This new medicine application is for a new biological entity, hereafter referred to as BNT162b2[mRNA] (Pfizer code number PF-07302048) or by the trade name Comirnaty, which has been developed by Pfizer and BioNTech. The drug product is an RNA-based vaccine indicated for the active immunisation of individuals aged 16 years and over against COVID-19 disease caused by the SARS-CoV-2 virus.

The drug substance is a nucleoside-modified single-stranded, 5'-capped mRNA that encodes a prefusion stabilised full-length variant of the SARS-CoV-2 spike (S) glycoprotein. The spike protein is a surface protein on the virus that binds to angiotensin converting enzyme 2 (ACE-2) on host cells. It is considered a relevant antigen for vaccine development as antibodies against the spike protein have been shown to neutralise the virus and prevent infection. The mRNA is produced using cell-free *in vitro* transcription from a DNA template encoding the viral spike protein. The RNAs are encapsulated in lipid nanoparticles (LNPs), which protect the RNA from degradation by RNases and facilitate entry of the RNA into host cells. The mRNA is translated into the SARS-CoV-2 S protein in the host cell cytosol, and is then expressed on the cell surface where it induces an adaptive immune response.

The vaccine is formulated as a preservative-free concentrated suspension for injection, presented in a multi-dose vial. The product is supplied frozen (-90°C to -60°C), and must be thawed and diluted with sterile sodium chloride (0.9%) solution prior to administration by intramuscular injection.

The NMA is being filed as a rolling submission in three waves, based on data availability at the time of submission. Section 1.11.3 confirms that with the exception of Module 1, the New Zealand dossier is identical to that submitted in Australia, the EU, the USA, Canada, Switzerland and Singapore. The EMA questions (and company responses) were provided in the second and third submissions to Medsafe, and are acknowledged in this report where applicable. The CHMP issued a positive opinion granting conditional marketing authorisation for distribution of Comirnaty in the EU on 21 December 2020, and relevant aspects of the CHMP EPAR are referenced in this report.

The EU approval is conditional on the provision of additional characterisation data for the drug substance and drug product, and the continuation of the pivotal Phase 3 clinical trial. The specific obligations of the conditional EU marketing authorisation (taken from the public EPAR), are shown in Attachment 1 of this report. The Medsafe assessment concurs with these obligations, which are considered critical to support the quality, safety and efficacy of the drug product produced at commercial scale. The CHMP also made several recommendations for future quality development (refer Attachment 2). Since the New Zealand dossier aligns with that registered in the EU, the company will be asked to commit to provide Medsafe with the same additional information requested by the CHMP. Additional questions specific to the New Zealand application have also been identified as outlined in this report.

As discussed in the Quality Assessment Conclusion section of this report, Medsafe will seek expert advice from the Medicines Assessment Advisory Committee (MAAC) to determine what information is required prior to approval for distribution in New Zealand, and what can be accepted post-approval.

RFI1 Q.1.	***Please commit to provide Medsafe with the same additional information (specific obligations) requested by the CHMP as part of the conditional marketing authorisation in the EU, where applicable. The commitments made to the EMA and FDA to review the drug substance and drug product specifications as additional data becomes available, should also be made to Medsafe. The sponsor should note that Medsafe will seek expert advice from***

the Medicines Assessment Advisory Committee (MAAC) to determine what additional information must be provided prior to approval for distribution of the vaccine in New Zealand, and what can be accepted post-approval.

EAI1 Q.1. *The applicant has provided the commitments as requested, and acknowledged that Medsafe will seek expert advice from the MAAC. Although the company has given a commitment to provide Medsafe with the same additional information required by the EMA's specific obligations, the EMA also had a list of 'recommendations' for additional data, some of which should also be provided to Medsafe post approval. Conditions of the New Zealand provisional consent for this product will include the same specific obligations for quality data as required by the EMA/CHMP, along with some of the EMA/CHMP quality data 'recommendations'. The specific conditions will be included in the provisional consent are listed in the Final Recommendation section of this report, and are considered essential to ensure that NMA quality data requirements are fulfilled within a reasonable time frame.* ***Point resolved****.*

The sponsor has confirmed by way of the signed declaration in the NMA form that the product is not a hazardous substance or a new organism in terms of the HSNO legislation, and does not require EPA approval prior to being released in New Zealand.

Product name

The proposed proprietary name for the product is COMIRNATY (presented in capital letters on the labels and in the data sheet). This is the same name as registered for the vaccine in the EU and Australia; however, the EU SPC refers to the vaccine as 'Comirnaty' (ie in sentence case rather than capitalised). For ease of readability, the evaluator has used 'Comirnaty' in this report. There are no other products approved in New Zealand that start with the letters 'Comi'. The name is not misleading in any way with regards to the nature, purpose, uses or effects of the product. The proposed name is acceptable.

Labelling

In the original dossier submission, the company submitted full scale colour artworks of the vial and carton labels that refer to the trade name as Pfizer-BioNTech COVID-19 Vaccine. In roll 2, updated labels were provided with the proposed trade name Comirnaty. The company is unable to say whether the initial supply of vaccine in New Zealand will be in the updated or original labels, so both are being registered with this NMA.

On 27/01/2021, additional labels were provided that reference delivery of 6 doses rather than 5 doses. The information provided to Medsafe as of 27/01/2021 is that the vaccine supplied to New Zealand is likely to be packaged in the labels that reference delivery of 6 doses. The evaluator notes that the TGA approved both 5 dose and 6 dose labels, so both will be approved with this NMA to ensure uninterrupted vaccine supply to the New Zealand market.

The proposed labelling and packaging have been developed for global distribution. The company has stated that once supply and demand become manageable, region-specific labelling will be created and incorporated into the supply chain.

Vial label version 1 (Pfizer-BioNTech COVID-19 Vaccine)

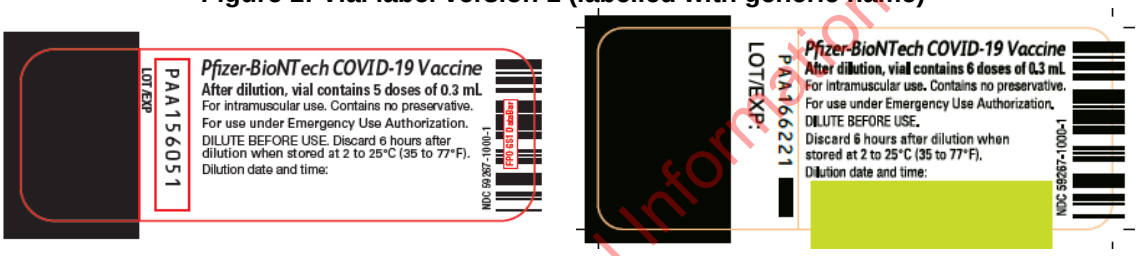
Since the proposed container is multidose, the vial label is subject to the full labelling requirements of regulation 13 of the New Zealand Medicines Regulations 1984. However, in alignment with the EU vaccine strategy, EMA/135540/2019 rev.4 *Recommendations for the implementation of the exemptions to the labelling and packaging leaflet obligations in the centralised procedure*, and EMA/616718/2020 *Questions and answers on labelling flexibilities for COVID-19 vaccines*, Medsafe will allow a labelling exemption to enable labelling and

packaging flexibilities for COVID-19 vaccines, to facilitate more rapid deployment of the product.

The information on the vial label proposed for initial global distribution of the vaccine (refer **Error! Not a valid bookmark self-reference.**) states the generic product name, batch number and expiry date, contents, and limited storage conditions. It does not mention the drug substance name or strength, but states that after dilution, the vial contains 5 doses of 0.3 mL. The absence of the statement of active substance has been allowed in principle by the EMA (pending suitable justification), as per EMA/616718/2020 (dated 27/11/2020). The label also includes a space for the vaccine administrator to write the date and time of dilution, and reminds the user to discard the product six hours after dilution. Although the vial (and carton) label refers to Emergency Use Authorization, which is not applicable in New Zealand, this is not considered a concern as it is clear this is a global medicine label (since it refers to storage conditions in °F), and distribution in New Zealand is contingent on Medsafe approval of the vaccine.

On 27/01/2021, an additional EU approved version of the label was provided that references delivery of 6 doses rather than 5 doses (right hand label).

Figure 1: Vial label version 1 (labelled with generic name)

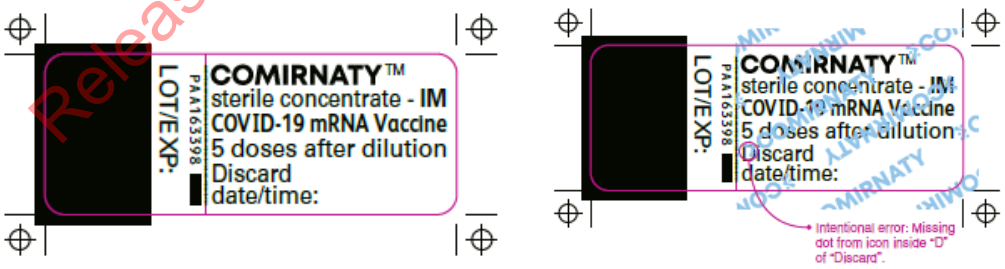


Vial label version 2 (Comirnaty)

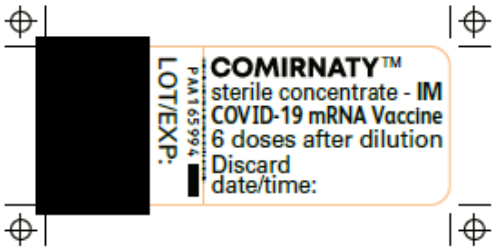
The vial labels with the proposed trade name are shown in **Error! Not a valid bookmark self-reference.**, with and without a varnish mock-up. There is even less information on the second version of the vial label; however, it still includes critical information such as the lot number, expiry date, and trade name. The evaluator notes that the first vial label has a space for writing the dilution date and time, whereas the second label has the discard date/time (ie 6 hours should be added to the dilution time). This difference has the potential to cause confusion so will need to be brought to the attention of vaccinators as part of a dear healthcare professional letter (DHPL). This is addressed in the below Request for Information (RFI).

Figure 2: Vial label version 2 (includes trade name Comirnaty)

5 doses



6 doses



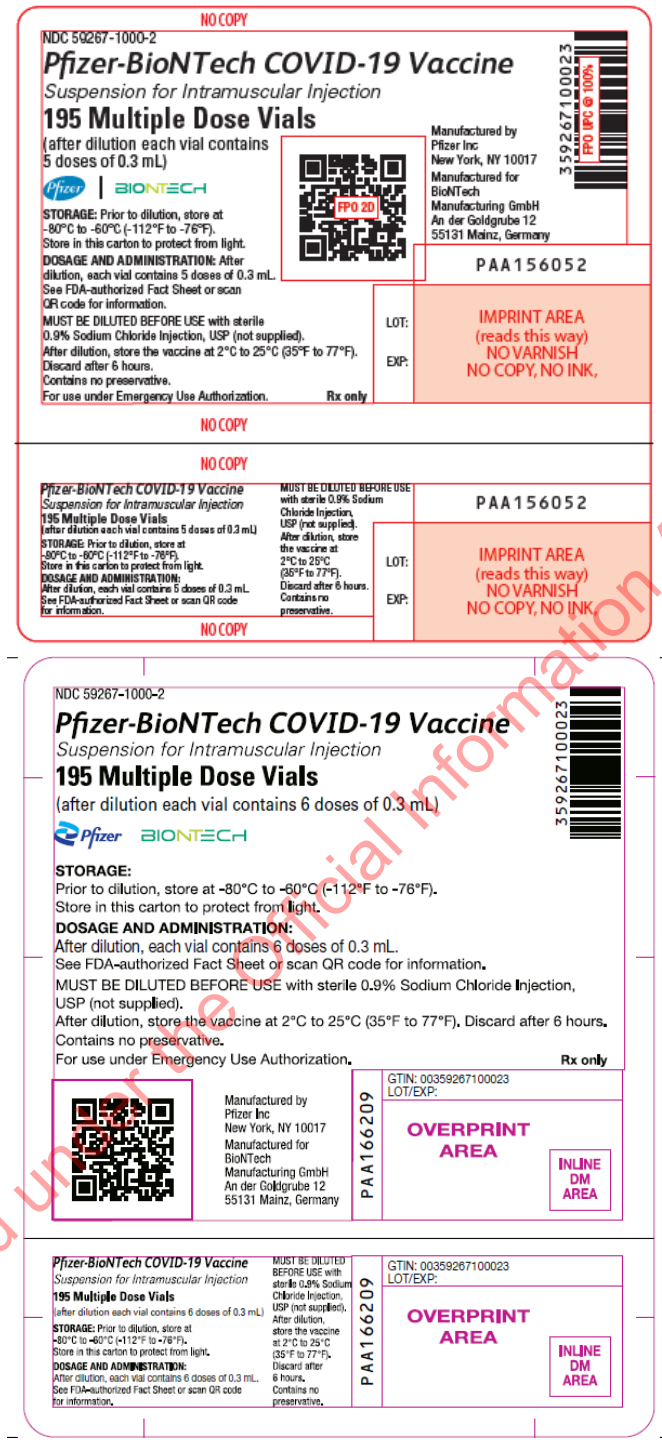
There is a note on the label artwork that the varnish is intentionally missing a dot from the icon inside 'D' of 'Discard'.

Carton label version 1 (Pfizer-BioNTech COVID-19 Vaccine)

The carton label with the generic product name proposed for initial global distribution of the vaccine is shown in Figure 3 and contains most of the information required by regulation 13 of the New Zealand Medicines Regulations 1984 for the labelling of medicines.

On 27/01/2021, an additional EU version of the label was provided (bottom label). A second version of the EU label was also provided that is identical to that shown in Figure 3 with the exception of the statement 'made in Germany' imprinted on it.

Figure 3: Carton label version 1 (labelled with generic name)



The following points are noted:

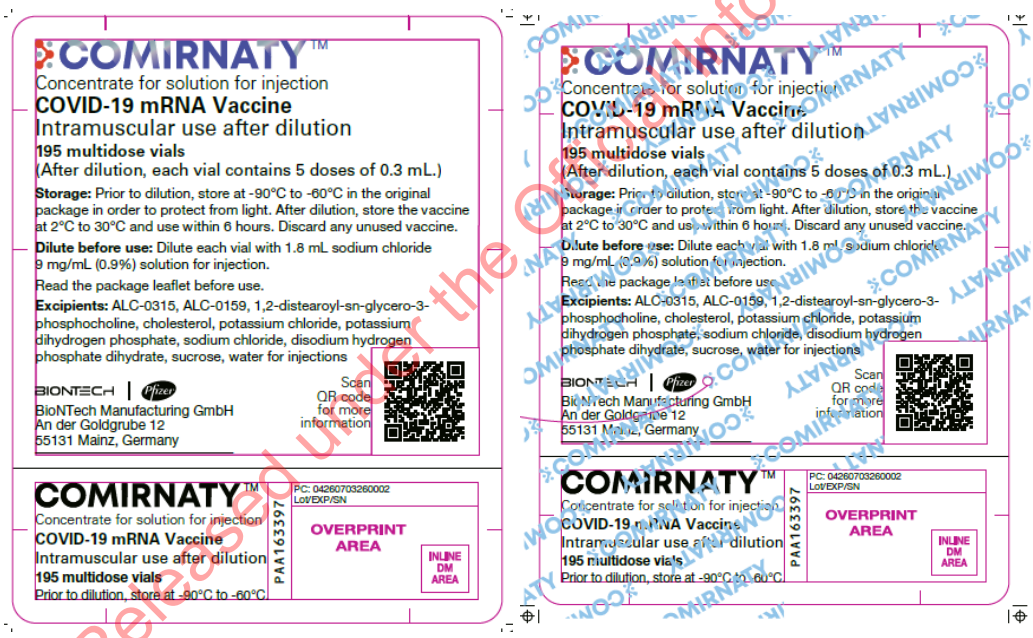
- the carton label does not state the name and strength/potency of the drug substance on either of the two panels
    - although this represents an area of non-compliance with New Zealand Medicines Regulations, the risk to patient safety as a consequence of the absence of this critical information is mitigated in part by the statement ‘each vial contains 5 doses of 0.3 mL’, which is repeated three times on the carton label
- the dose form description on the carton label is ‘suspension for intramuscular injection’ and does not mention that the product is a vaccine concentrate

  - this is not considered a significant safety concern, as the label clearly describes a requirement for dilution with 0.9% Sodium Chloride Injection, USP' (not supplied) before use

- the label includes the statement 'Rx only', which is recognised in New Zealand as meaning the product is a Prescription Only medicine
- the labels states the storage conditions for the unopened, undiluted product (-80 to -60°C, protect from light), and following dilution (2 to 25°C for up to 6 hours); the labels do not state the intermediary storage condition for the thawed but not yet diluted product (ie room temperature for no more than 2 hours, or in the refrigerator at 2 to 8°C for up to 5 days
- the Dosage and Administration information on the label directs the user to see the 'FDA-authorized Fact Sheet (the package insert) or to scan the QR code
  - The QR code links to the URL https://www.pfi.sr/pfebntcovidvax, which contains global information about the vaccine, with links to country specific information on administration. The company has been asked to confirm that New Zealand will be included in the list of countries after approval; refer RFI1 Q.2).

Carton label version 2 (Comirnaty)
The carton labels with the proposed trade name are shown in Figure 4, with and without a varnish mock-up.

Figure 4: Carton label version 2 (includes trade name Comirnaty)



Carton label version 2 (includes trade name Comirnaty) *cont*.

In the dossier update received 13/01/2021, the dose form description on the carton label was updated from 'concentrate for solution for injection' (top labels) to 'concentrate for dispersion for injection' (bottom labels).

On 27/01/2021, the label was updated to reference delivery of 6 doses (right hand bottom label) rather than 5 doses (remaining labels).

In email correspondence received 28/01/2021 the company confirmed that the carton labels received 13/01/2021 and 27/01/2021 are proposed to be used on the vaccine supplied to New Zealand. Any future changes to the labels will be submitted for Medsafe approval, as per normal regulatory requirements. The company also confirmed that the blue varnish 'COMIRNATY' on the labels is transparent and does not impact the legibility of the text on the labels. This is acceptable.

The updated carton labels with the Comirnaty trade name differ from the original labels with regards to the product name, dose form description ('concentrate for solution for injection' versus 'suspension for intramuscular injection'), and storage temperature ranges (unopened: -90°C to -60°C versus -80°C to -60°C; diluted: 2°C to 30°C versus 2°C to 25°C). Version 2 of the label no longer refers to emergency authorization and refers simply to dilution with sodium chloride rather than requiring USP saline. The QR code links to a splash page (https://www.pfi.sr/comirnatyglobal) that requires the user to select their country of origin to access information specific to their location. Currently, the splash page and listed countries appear specific to the EU approval of the vaccine (the QR code on the original label links to a more generic splash page that provides global information on the vaccine). The company will be asked to confirm that New Zealand will be added to the list of countries linked to from both QR codes following approval.

RFI1 Q.2. ***Please confirm that New Zealand will be included in the list of countries for region specific product information accessed via the QR codes on the proposed carton labels, and describe what information will be linked to from these webpages (eg the current approved New Zealand data sheet for Comirnaty). Since the information forms part of the registered product details for this vaccine, any changes to the content held at the URLs post-approval that is relevant to the product marketed in New Zealand should be***

communicated to Medsafe via the changed medicine notification (CMN) process.

EAI1 Q.2. *The applicant has explained that the QR codes connect to either the cvdvaccine.com or www.comirnatyglobal.com website. From there the individual accessing the website can select 'Health care professional' or 'Not a health care professional' and the specific country in which they are located, e.g. New Zealand. The applicant states that the website then directs to the locally approved label/data sheet. Although a data sheet is appropriate for health care professionals, the applicant has not explained what information a non-health care professional will be directed to.* ***This needs to be clarified as part of the outcome of evaluation but need not delay approval of this NMA.*** *The applicant has confirmed that Medsafe will be notified via CMN of any changes to the content on the URL that is relevant to product marketed in New Zealand.*

The following areas of non-compliance require a labelling exemption:

- the dose form is incorrectly described as a concentrate solution for injection, whereas is should be described as a concentrate suspension for injection (if the carton label supplied on 13.01.2021 is the label intended for the New Zealand market, then the description of the dose form as 'concentrate for dispersion for injection' is acceptable and does not require a labelling exemption)
- the carton labels do not include the name and strength of the active ingredient
- the absence of a classification statement
- the storage conditions are incomplete and do not include thawing conditions (time and temperature). Considering storage conditions are critical to the stability of this product, thawing conditions should also be included on the label

The evaluator also notes the statement in the fact sheet/package insert that 'some vials and cartons of Pfizer-BioNTech COVID-19 vaccine multiple dose vial may be labelled as BNT 162b2 (SARS-COV-2-mRNA vaccine) 5-dose vial'. Although these latter labels are not proposed for New Zealand, the fact they are referenced in a package insert that could be supplied in this country means that this should also be noted in a Dear Healthcare Professional Letter (DHPL) that accompanies release of this product to the New Zealand market. The company will be asked to provide a DHPL for review, that addresses the below points.

RFI1 Q.3. ***Since the first shipments of vaccine for the New Zealand market will be supplied in international labelling that does not comply fully with New Zealand medicines regulations, the company is asked to provide a 'Dear Healthcare Professional Letter' to accompany release of the product. Information included in the letter should address (but is not limited to) the following:***
i) The letter should identify the international labelling that will be used for distribution of the vaccine in New Zealand. The inclusion of colour photograph(s)/artwork(s) of the labels in the letter is encouraged. If both versions of the labels will be used, differences between the labels should be identified. For example, on one set of labels the administrator is informed to write the <u>dilution</u> date/time, whereas the other label set requires the administrator to write the <u>discard</u> date/time.
ii) Depending on what version of the labels will be used, the company should clarify that the statement 'For use under Emergency Use Authorization' on the US labels is not relevant to New Zealand, that the sodium chloride used for dilution can be Ph. Eur. quality (not just USP quality), and to explain reference to labelling of some vials as 'BNT 162b2 (SARS-COV-2-mRNA vaccine) 5-dose vial' (as mentioned in the fact sheet/package insert) is not

	relevant to New Zealand. ***iii) Clear storage conditions should be provided on the letter, including storage conditions for frozen, thawed/unopened product and diluted product. This is of particular importance, as the intermediary storage condition (ie for the thawed but not yet diluted product), is not listed on the label.*** ***Please provide (or commit to do so prior to launch of the vaccine to the New Zealand market), a draft DHPL that addresses the above concerns.***
EAI1 Q.3.	*The applicant has indicated that a 'Dear Healthcare Professional' letter is being prepared and will be provided to Medsafe prior to launch of this vaccine. The company will be informed that the letter should also address the requirement for the use of low dead-volume syringes and needles in order to extract 6 doses from a single vial (this change was introduced on 27/01/2021). The DHPL should also reiterate that if the amount of vaccine remaining in the vial after the fifth dose cannot provide a full dose (0.3 mL), the healthcare professional must discard the vial and its contents. There should be no pooling from multiple vials to make up a full dose, and any unused vaccine should be discarded 6 hours after dilution.* ***It is critical that Medsafe receives and reviews this letter prior to marketing of this vaccine. The provisional consent for this product will include the requirement to prepare a Dear Healthcare Professional letter and provide this to Medsafe for review and approval prior to distribution of this product.***

Labelling exemption

On the basis that i) the proposed vaccine has been developed in response to the current global COVID-19 pandemic, and ii) will be supported by a comprehensive information programme for New Zealand healthcare professionals, the company's request for a labelling exemption for the noted areas of non-compliance will be granted. The labelling exemption for the two sets of international vial and carton labels will be valid for the duration of the s23 approval granted at gazettal of this NMA, or until approval of New Zealand specific labelling, whichever occurs first.

Data sheet and package insert

A draft New Zealand data sheet was provided with roll 2. Medsafe's assessment of the clinical information in the data sheet is documented in a separate report.

The data sheet mostly complies with New Zealand medicines regulations requirements. The following points were noted from assessment of the roll 2 information:

i) The data sheet refers to the product as Comirnaty, BNT162b2, COVID-19 vaccine. Consistent reference to the trade name 'Comirnaty' is required.

ii) *Section 1*: It is considered incorrect to refer to the strength as 30 µg/0.3 mL next to 'concentrated suspension for injection' as this is the strength of the diluted vaccine (ie the strength of the undiluted vaccine is 0.5 mg/mL).

iii) *Section 2*: The statement 'One vial contains 5 doses of 30 micrograms (0.45 mL of BNT162b2 [mRNA]) embedded in lipid nanoparticles' is considered confusing, and should be revised to state 'One vial (0.45 mL) contains 5 doses of 0.3 mL after dilution. One dose (0.3 mL) contains 30 micrograms of COVID-19 mRNA vaccine embedded in lipid nanoparticles'

iv) *Section 4.2*: For clarity, a separate heading for 'Elderly population' should be added, with the statement 'No dosage adjustment is required in elderly individuals ≥ 65 years of age'.

v) *Section 5.1*: The ATC code J07BX should be added as per the EU SPC.

vi) *Section 6.3*: For clarity, information in this section should include both the unopened vial and the diluted medicinal product, as per the EU SPC for Comirnaty.

In roll 3, received 8/01/2021, an updated data sheet was provided that addressed the points raised in i), iii), iv), v) and vi). One additional change is still required as detailed below. As part of the data sheet update, the company revised the storage and handling information to align with the EU SPC for Comirnaty (includes pictorials as part of the instructions). This is acceptable.

RFI1 Q.4. ***Please make the following change to the proposed data sheet:***
i) Section 1: Please change the strength description of the vaccine concentrate to 0.5 mg/mL, as 30 µg/0.3 mL is the strength of the diluted vaccine.

EAI1 Q.4. *The data sheet has been updated as requested. The data sheet has also been updated to include the following:*

- an additional statement regarding use in children and adolescents less than 16 years of age, i.e. "Limited data are available in this age group".

- a traceability statement in section 4.4. 'Special warnings and precautions for use', "In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded". The applicant states that the statement was included at the request of the TGA. Although the New Zealand data sheet is published separately to the TGA approved Product Information, inclusion of this statement is acceptable.

-editorial change to the statement in section 4.4. regarding close observation is recommended following vaccination.

The proposed changes are acceptable. ***Point resolved****.*

s 6(b)(ii)

[redacted]

On 27/01/2021, Medsafe received a request from the company to revise the number of doses that can be delivered from a single vial from 5 doses to 6 doses. The information provided in support of the delivery of 6 doses is discussed in section 3.2.P.2.2 of this report. The proposed change has been approved by both the EMA and the TGA. Applicable sections of the data sheet and CMI have been updated to reference the 6 doses. Notably, the revised data sheet (and current EU approved SPC for Comirnaty) describe a requirement for the use of low dead-volume syringes and/or needles (no more than 35 µL dead volume) to extract 6 doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from the vial. The data sheet instructs the user to discard the vial if the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL. ***A requirement for the use of low dead-volume syringes and needles in order to extract 6 doses from a single vial should be noted in the DHPL that will accompany release of the vaccine to the New Zealand market. The DHPL should also reiterate that if the amount of vaccine remaining in the vial after the fifth dose cannot provide a full dose (0.3 mL), the healthcare professional must discard the vial and its contents. There should be no pooling from multiple vials to make up a full dose, and any unused vaccine should be discarded 6 hours after dilution.***

The international medicine pack with the generic product name ('version 1') will be supplied with a fact sheet that details how the vaccine should be used. Although referred to as a

global document, the fact sheet is targeted towards the US market, as it refers to the US FDA Emergency Use Authorization (EUA) of the unapproved product, and the FDA mandatory requirements for use under the EUA. The document directs the user to www.cvdvaccine.com for the most recent version of the fact sheet. This is the same webpage as the one linked to from the QR code on the label.

With the exception of the indicated age range (the fact sheet refers to use in individuals 18 years of age and older, whereas the company is seeking approval to administer to individuals in New Zealand aged 16 years and over), the dosage and administration information (presented graphically and with text descriptions) aligns with the details proposed in this NMA. The fact sheet notes that there are no data available on the interchangeability of the Pfizer-BioNTech COVID-19 vaccine with other COVID-19 vaccines to complete the vaccination series (two doses). The quality details in the fact sheet (formulation, storage, in use shelf-life) align with the product details proposed for registration in New Zealand.

Consumer medicines information (CMI) was provided in roll 2 and roll 3, and updated on 27/01/2021 to reflect the delivery of 6 doses rather than 5 doses. The information in the CMI aligns with that in the data sheet. The sponsor has signed the CMI commitment in the NMA form that following consent to distribute, an electronic copy of the CMI will be submitted to Medsafe and will comply with the requirements published on the Medsafe website.

GMP status of manufacturers and packers

The applicant has provided the following evidence of GMP compliance for the drug substance and drug product manufacturing, testing and packaging sites.

Table 1: Proposed manufacturing sites and GMP status

Manufacturing step	Site address	Authority	Certificate number	Expires
Drug substance manufacture and testing	BioNTech Manufacturing GmbH, An der Goldgrube 12, Mainz 55131, GERMANY	TGA	MI-2020-CL-10905-1 Authorises the site for active material manufacture of BNT162b2 (mRNA) and testing (sterility)	**9/01/2024**
	Rentschler Biopharma SE, Erwin-Rentschler-Strasse 21, Laupheim 88471, GERMANY	TGA	MI-2020-CL-10912-1 Authorises the site for active material manufacture of BNT162b2 (mRNA) and testing (biological, chemical and physical, endotoxin), packaging and storage	**31/03/2021**
	Wyeth Biopharma, Division of Wyeth Pharmaceuticals LLC, 1 Burtt Road, Andover, Massachussetts 01810, USA	TGA	MI-2020-CL-11475-1 Authorises the site for active material manufacture of BNT162b2 drug substance and COVID-19 vaccine endotoxin testing	**18/07/2022**

	Pfizer Inc, 875 Chesterfield Parkway West, Chesterfield, MO 63017-1732, USA	TGA	MI-2020-CL-10943-1 Authorises the site for testing (analytical, biological, chemical and physical, endotoxin) of sterile dosage forms and API (not defined)	**20/02/2022**
	BioNTech Innovative Manufacturing Services GmbH, Vollmersbachstrasse 66, Idar-Oberstein 55743, GERMANY	TGA	MI-2020-CL-10909-1 Authorises the site for testing (sterility, chemical and physical, biological, microbial) and irradiation of BNT162b2 mRNA	**30/04/2023**
	Pfizer Manufacturing Belgium NV, Rijksweg 12, Puurs B-2870, BELGIUM	TGA	MI-2020-CL-04395-1 Authorises the site for sterile finished product manufacture of injections, and testing (sterility, biological, endotoxins)	**31/12/2021**
Drug product manufacture, packaging and testing	s 9(2)(b)(ii) [redacted]			
	Pfizer Ireland Pharmaceuticals, Grange Castle Business Park, Clondalkin, Dublin 22, IRELAND	TGA	MI-2017-CL-00823-1 Authorises the site for sterile finished product manufacture and testing (microbial, biological, chemical and physical)	**9/05/2022**
Finished product testing only	Wyeth Biopharma, Division of Wyeth Pharmaceuticals LLC, 1 Burtt Road, Andover, Massachussetts 01810, USA	TGA	MI-2020-CL-02177-1 Authorises the site for testing (chemical and physical, biological, microbial, sterility)	**18/07/2022**
	Pfizer Inc, 875 Chesterfield Parkway West, Chesterfield, MO 63017-1732, USA	TGA	MI-2020-CL-10943-1 Authorises the site for testing (biological, chemical and physical, analytical, endotoxin) of sterile dosage forms and API (not defined)	**20/02/2022**

	Hospira Zagreb Ltd, Prudnicka cesta 60, Prigorje Brdovecko 10291, CROATIA	TGA	MI-2017-CL-13674-1 Authorises the site for sterile finished product manufacture, secondary packaging and testing (sterility, biological)	**22/09/2022**
	SGS Lab Simon SA, Vieux Chemin du Poete 10, Wavre B-1301, BELGIUM	TGA	MI-2017-CL-03231-1 Authorises the site for testing (chemical and physical, sterility, biological and microbial)	**31/12/2021**

The drug product manufacturing sites Pharmacia & Upjohn Company LLC, BioNTech Manufacturing GmbH and Pfizer Pharma GmbH are not proposed for the initial registration of the product in New Zealand.

The GMP evidence is acceptable. **The company will be reminded as part of the outcome of evaluation email to provide updated evidence of cGMP for Rentschler Biopharma SE, Erwin-Rentschler-Strasse 21, Laupheim 88471, Germany, when available, as the current clearance will expire on 31/03/2021.**

Module 3.2.S. Drug Substance

Background

Several drug substance variants were investigated in the Pfizer/BioNTech non-clinical and Phase 1 COVID-19 vaccine clinical studies (refer below table).

Table 2: Drug substance candidates used in non-clinical and Phase I clinical studies

BNT162 vaccine candidate	RNA platform	Encoded antigen
s 9(2)(b)(ii)		
BNT162b2	Nucleoside Modified mRNA	Full length SARS-CoV-2 spike protein bearing mutations preserving neutralisation-sensitive sites
s 9(2)(b)(ii)		

On the basis of available safety and immunogenicity data (recipients demonstrated a favourable breadth of epitopes specific to the spike antigen, and concurrent induction of high magnitude CD4+ and CD8+ T cell responses against the receptor binding domain (RBD)), the variant BNT162b2 [mRNA] was selected to progress through to Phase 2/3 of the pivotal clinical study (C4591001).

The manufacture, characterisation and quality control of BNT162b2 [mRNA], is assessed in this report. At times reference is also made to the available data for BNT162b1, as supportive evidence.

3.2.S.1 General information

The drug substance, BNT162b2, is a single-stranded messenger RNA (mRNA), encoding a full-length, codon-optimised, pre-fusion stabilised conformation variant (K986P and V987P) of the SARS-CoV-2 spike (S) glycoprotein (the antigen).

3.2.S.1.1 Nomenclature

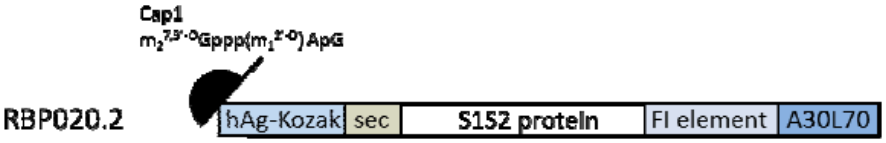
Table 3: Nomenclature of BNT162b2 drug substance

Product code:	BNT162b2
Laboratory code:	RBP020.2; ($m_2^{7,3'-O}$Gppp($m_1^{2'-O}$)ApG)-hAg-Kozak-S1S2-PP-FI-A30L70
Chemical class:	Ribonucleic Acid (RNA)
Encoded antigen:	Viral spike protein (S1S2 protein) of the SARS-CoV-2 (S1S2 full-length protein, containing two mutations: K986P and V978P)
CAS Registry Number:	2417899-77-3
CA Index Name:	RNA (recombinant 5'-[1,2-[(3'-O-methyl)m7G-(5'->5')-ppp-Am]]-capped all uridine->N1-methylpseudouridine-substituted severe acute respiratory syndrome coronavirus 2 secretory signal peptide contg. spike glycoprotein S1S2-specifying plus 5'- and 3-untranslated flanking region-contg. poly(A)-tailed messenger BNT162b2), inner salt
INN	Tozinameran (proposed INN)

3.2.S.1.2 Structure

A schematic illustration of the general structure of the BNT162b2 [mRNA] drug substance is shown below (not drawn to scale with regards to sequence lengths).

Figure 5: General structure of BNT162b2 [mRNA]



The structure is determined by the respective nucleotide sequence of the DNA used as the template for *in vitro* RNA transcription.

RNA sequence

The full sequence of BNT162b2 is shown in Attachment 3, and is based on the sequence of the 'Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1' (GenBank entries: MN908947.3 (complete genome), QHD43416.1 (spike surface glycoprotein)). The sequence length is 4284, which includes G to denote the presence of the 5'-cap analog (G: 1062, C: 1315, A: 1106, Y: 801). The company will be asked to comment on the RNA sequence in context of the B.1.1.7 (VOC-202012/01) and B.1.351 (501Y.V2) variant strains of SARS-CoV-2.

s 9(2)(b)(ii)

[redacted]

s 9(2)(b)(ii)

[redacted]

In addition to the codon-optimised sequence encoding the antigen, the RNA contains structural elements for mediating RNA stability and translational efficiency (5'-cap, 5'-UTR (hAg-Kozak), 3'-UTR (FI element), 3' poly(A)-tail (A30L70)). Furthermore, an intrinsic signal peptide (sec) is part of the open reading frame and is translated as an N-terminal peptide. Selection of the sequence elements was guided by the company's experience working with RNA transcripts, and the scientific literature (references provided). Key details of each of these elements are summarised as follows:

hAg-Kozak (nucleotides 2 to 54): 5'-UTR sequence of the human alpha-globin mRNA with an optimised 'Kozak sequence' to increase translational efficiency.

Sec (nucleotides 55 to 102): Corresponds to the intrinsic S1S2 protein signal peptide (sec), which guides translocation of the nascent polypeptide chain into the endoplasmic reticulum.

S1S2 protein (nucleotides 103 to 3879): Codon-optimised sequence encoding the spike antigen of SARS-CoV-2. The S1S2 protein or spike glycoprotein is expressed on membranes and facilitates recognition by the host cells, as well as cellular uptake. The protein sequence contains two proline mutations (K986P and V987P), which ensure an antigenically optimal pre-fusion confirmation (P2 S).

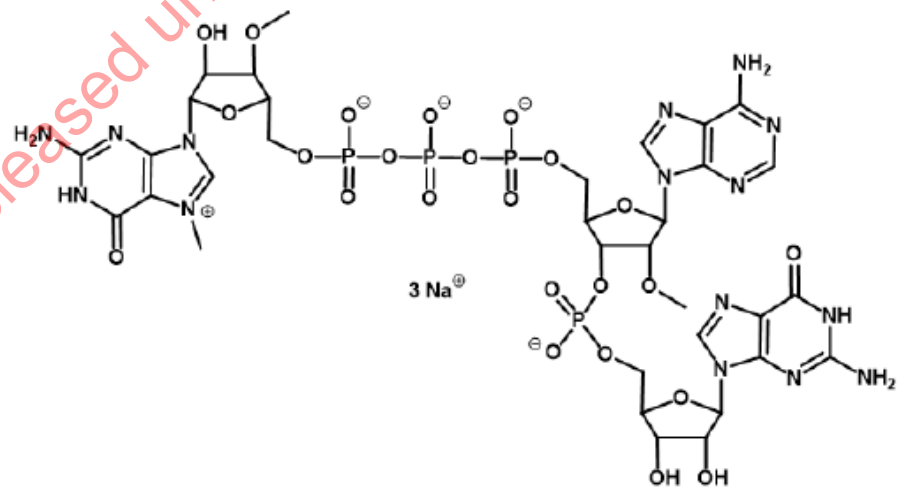
FI element (nucleotides 3880 to 4174): The 3′-UTR is a combination of two sequence elements derived from the amino terminal enhancer of split (AES) mRNA (called 'F') and the mitochondrial encoded 12S ribosomal RNA (called 'I'). These were identified by an *ex vivo* selection process for sequences that confer RNA stability and augment total protein expression.

A30L70 (nucleotides 4175 to 4284): A poly(A)-tail measuring 110 nucleotides in length, consisting of a stretch of 30 adenosine residues, followed by a 10 nucleotide linker sequence and another 70 adenosine residues. The poly(A)-tail is designed to enhance RNA stability and translational efficiency in dendritic cells.

mRNA cap

The 5' cap protects the drug substance from exonucleolytic activity and promotes translation of the protein antigen *in vivo*. The structure of the 5' mRNA cap (cap1) is shown below.

Figure 6: 5'-cap analog ($m_2^{7,3'\text{-O}}$Gppp($m_1^{2'\text{-O}}$)ApG)



The cap1 structure (containing a 2′-O-methyl group on the penultimate nucleoside of the 5′-end of the RNA chain) is incorporated into the BNT162b2 drug substance during *in vitro* transcription. For RNAs with modified uridine nucleotides, the cap1 structure is superior to other cap structures because cap1 is not recognised by cellular factors such as IFIT1.

Consequently, cap1-dependent translation is not inhibited by competition with eukaryotic translation initiation factor 4E. In the context of IFIT1 expression, mRNAs with a cap1 structure give higher protein expression (based on the available literature and manufacturing experience).

Use of the cap1 structure also leads to low amounts of uncapped transcripts. In general, the T7 polymerase prefers a guanosine as the priming nucleoside, leading to higher transcription efficiencies as compared to other starting nucleosides. Capping structures with a guanosine moiety compete with GTP for incorporation in the mRNA resulting in uncapped transcripts. The $m_2{}^{7,3'\text{-O}}$Gppp($m_1{}^{2'\text{-O}}$)ApG cap analog rescues transcription efficiency from templates starting with adenosines, because the ApG moiety of cap1 allows transcription initiation at the second position, a guanosine, thereby giving mainly capped mRNAs.

Modified uridine

The RNA does not contain any uridines. During synthesis of the RNA, the modified N1-methylpseudouridine triphosphate ($^{m1}\Psi$TP) is used in place of uridine triphosphate (UTP). This substitution has been made to enhance translation of the *in vitro* transcribed mRNA sequences by reducing its immunogenicity.

3.2.S.1.3 General properties

The BNT162b2 drug substance is formulated at a target concentration of 2.25 mg/mL in drug substance formulation buffer (10 mM HEPES, 0.1 mM EDTA, pH 7.0). The general properties of the drug substance are shown below.

Table 4: BNT162b2 drug substance general properties

Appearance	Clear to slightly opalescent, colorless to slightly brown liquid
Specific Absorption Coefficient (260 nm)	25 L/g × cm
Theoretical length[a]	4,283 nucleotides
Theoretical mass[b]	1,388,651 g/mol
pH	Target 7.0

a. Theoretical value has been verified by gel electrophoresis compared to a size marker. The length is 4,284 nucleotides when the presence of the 5'-cap analog (G) is included.
b. Theoretical value has been verified indirectly by control of RNA lengths.

The structural and functional studies conducted to characterise BNT162b2 are discussed later in this report.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturers

The following table summarises the responsibilities of the sites involved in the production of the BNT162b2 drug substance. Although three drug substance manufacturing sites are proposed, the Rentschler and BioNTech, Mainz (BNT Mainz) sites each perform different steps in the manufacturing process, contributing to the production of a single batch of drug substance.

Table 5: Manufacture and testing sites associated with the production of BNT162b2

Site	Responsibility
Wyeth BioPharma Division of Wyeth Pharmaceuticals, LLC [a] 1 Burtt Road Andover, MA 01810 United States	Manufacture of drug substance Release and Stability Testing (Composition, Strength, Identity, Purity, Process Related Impurities, Safety)
Pfizer Inc 875 Chesterfield Parkway West Chesterfield, MO 63017 United States	Release and Stability Testing (Composition, Strength, Identity, Purity, Process Related Impurities)
BioNTech Manufacturing GmbH An der Goldgrube 12 55131 Mainz Germany	Manufacture of drug substance (In-vitro Transcription, DNase I and Proteinase K digestion) Release and Stability Testing (Identity, Purity, Process Related Impurities)
Rentschler Biopharma SE Erwin-Rentschler-Str. 21 88471 Laupheim Germany	Manufacture of drug substance (Ultrafiltration/Diafiltration (UFDF), DS Dispensing) Release and Stability Testing (Composition, Strength, Safety)
BioNTech Innovative Manufacturing Services GmbH Vollmersbachstraße 66 55743 Idar-Oberstein Germany	Release and Stability Testing (Product Related Impurities, Purity)

a. The legal entity name change from Wyeth BioPharma Division of Wyeth Pharmaceuticals was changed at the acquisition by Pfizer in 2009, since then the Wyeth Pharmaceuticals manufacturing site in Andover, Massachusetts belongs to Pfizer's production sites and is embedded in Pfizer's GMP system. Pfizer will be utilized throughout the CTD.

The manufacturing processes and process parameters applied at Andover and BNT Mainz/Rentschler are slightly different, so are described separately in this report.

3.2.S.2.2 Description of manufacturing process and process controls

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[redacted]

Module 3.2.P. Drug Product

3.2.P.1. Description and composition of the drug product

The drug product is a preservative-free white to off-white frozen sterile dispersion of RNA-containing lipid nanoparticles (LNPs) in aqueous cryoprotectant buffer (phosphate buffered saline and 300 mM sucrose at pH 7.4). The drug product is presented as a multi-dose concentrate in a clear glass 2 mL clear vial (type I glass), sealed with a synthetic bromobutyl rubber stopper, aluminium overseal and plastic flip-off cap. Each vial contains 0.45 mL of drug product and is designed to contain a total of 6 doses ~~5 doses~~ of 30 µg of RNA in 0.3 mL after thawing and dilution with 1.8 mL of sterile 0.9% sodium chloride injection (total volume of 2.25 mL). The drug product is administered by intramuscular injection.

A copy of the full formulation and quality standards applied to the excipients as detailed in the dossier is shown in Table 54. The formulation details as recorded in Medsafe's SMARTI database are also included in the attached Therapeutic Product Database Report.

Table 54: Formulation details of BNT162b2 drug product
Updated in roll 3

Name of Ingredients	s 9(2)(b)(ii)
BNT162b2 drug substance	
ALC-0315	
ALC-0159	
DSPC	
Cholesterol	
Sucrose	
Sodium chloride	
Potassium chloride	
Dibasic sodium phosphate, dihydrate[b]	
Monobasic potassium phosphate[c]	
Water for Injection	
Processing Aids/Resi	
Ethanol	
Citric acid monohydrate	
Sodium citrate	
Sodium hydroxide	
HEPES	
EDTA	

a. Values are rounded to maintain the same level of precision as the label claim, with trailing zeros not shown, where applicable. s 9(2)(b)(ii)
b. Dibasic sodium phosphate, dihydrate is named as disodium phosphate dihydrate in the Ph. Eur.
c. Monobasic potassium phosphate is named as potassium dihydrogen phosphate in the Ph. Eur.
d. The processing aids and drug substance formulation buffer components are residues that are essentially removed through the manufacturing process are not considered ingredients (excipients).
Abbreviations:
ALC-0315 = ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide
DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine
q.s. = quantum satis (as much as may suffice)
HEPES = 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
EDTA = edetate disodium dihydrate

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3.2.P.2. Pharmaceutical development

The pharmaceutical development of BNT162b2 utilised principles described in ICH Q8, risk assessments, development studies and prior experience with similar RNA-lipid nanoparticle vaccines.

3.2.P.2.1. Components of the drug product

3.2.P.2.1.1. Drug substance

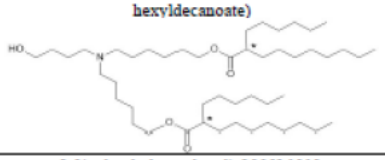
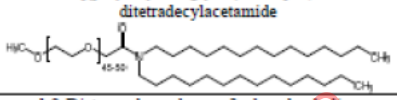
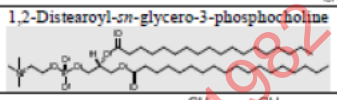
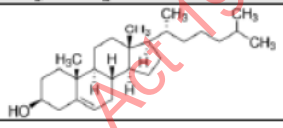
The drug substance (RNA) is provided for drug product manufacture as a frozen (-20 ± 5°C) aqueous solution (2.25 ± 0.25 mg/mL) in 10 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), 0.1 mM edetate disodium dihydrate (EDTA) at pH 7.0.

There are no obvious compatibility issues between the drug substance and the excipients present in the drug product formulation.

3.2.P.2.1.2. Excipients

The drug product contains RNA LNPs formulated in a phosphate-buffered saline (chosen for its ability to provide adequate buffering capacity at physiological pH), and 300 mM (103 mg/mL) sucrose (chosen as a cryoprotectant for frozen storage) at target pH 7.4. The drug product also contains four lipids that play a functional or structural purpose in the assembly and/or enable stabilisation of the RNA LNP. DSPC and cholesterol are structural lipids, providing a stable bilayer and enabling mobility of the lipid components within the LNP structure. ALC-0315 is an ionisable cationic lipid that is critical for successful delivery of RNA, ensuring the self-assembly of the LNP, the uptake of the LNP into the cells, and the escape of the RNA from the endosome. ALC-0159 is a PEGylated lipid that inserts itself in the outer lipid bilayer of the LNP, thereby providing a steric barrier to interactions with surfaces or other LNP that could result in particle fusion during storage. The structures of the lipid components are shown below. The nonclinical and clinical safety data for drug product containing these lipids is reviewed in separate Medsafe reports.

Table 55: Lipid components of the drug product

Lipid	Concentration (mg/mL)	Molecular Weight [Da]	Molecular Formula	Chemical Name (Synonyms) and Structure
ALC-0315[a]	7.17	766	$C_{48}H_{95}NO_5$	((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) 
ALC-0159[b]	0.89	~2400-2600	$(C_2H_4O)_nC_{31}H_{63}NO_2$ n=45-50	2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide 
DSPC[c]	1.56	790	$C_{44}H_{88}NO_8P$	1,2-Distearoyl-*sn*-glycero-3-phosphocholine 
Cholesterol[d]	3.1	387	$C_{27}H_{46}O$	

a. CAS Number 2036272-55-4
b. CAS Number 1849616-42-7
c. CAS Number 816-94-4
d. CAS Number 57-88-5
Asterisks (*) indicate chiral centers for ALC-0315

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[redacted]

Pages 80 - 125 withheld under section 9(2)(b)(ii) of the Act.

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Attachments

1. Therapeutic Product Database Report
2. Quality Evaluation Report Attachments
3. Novel Excipients Evaluation Report
4. Non-Clinical Evaluation Report
5. Clinical Evaluation Report

References

Collier, D.A., Meng, B., Ferreira, I.A.T.M, et al. Impact of SARS-CoV-2 B.1.1.7 Spike variant on neutralisation potency of sera from individuals vaccinated with Pfizer vaccine BNT162b2. medRxiv preprint doi: https://doi.org/10.1101/2021.01.19.21249840 (2021).

Sahin U, Muik A, Vogler I et al. BNT162b2 induces SARS-CoV-2-neutralising antibodies and T cells in humans. medRxiv preprint doi: https://doi.org/10.1101/2020.12.09.20245175

Wang, Z., Schmidt, F., Weisblum, Y., et al. mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants. bioRxiv preprint doi: https://doi.org/10.1101/2021.01.15.426911 (2021)

Wibmer, C. W., Ayres, F., Hermanus, T., et al. SARS-CoV-2 501Y.V2 escapes neutralisation by South African COVID-19 donor plasma. bioRxiv preprint doi: https://doi.org/10.1101/2021.01.18.427166 (2021).

Xie X, Zou J, Fontes-Garfias C et al. Neutralization of N501Y mutant SARS-CoV-2 by BNT162b2 vaccine-elicited sera. bioRxiv preprint https://doi.org/10.1101/2021.01.07.425740

Final Recommendation

A number of quality issues, and some clinical issues arising from this application still remain unresolved. The applicant has committed to providing the outstanding information to address these issues, with many of these issues aligning with the EMA/CHMPs specific obligations that were listed in the EU's conditional approval. Due to this outstanding information the product cannot be recommended for consent under Section 20 of the Medicines Act 1981 for distribution in New Zealand. However, due to the COVID-19 global pandemic situation and the clinical need for the product, provisional consent under Section 23 of the Medicines Act 1981 may be considered for the following indication:

COMIRNATY is indicated for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 16 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

It is proposed that any provisional consent include the following conditions:

Provisional consent is to be granted for a period of nine months to address an urgent clinical need.

Provisional consent may only be renewed if the sponsor fulfils the following obligations within specified timelines, the dates of which may be altered on mutual agreement between Medsafe and the sponsor:

1) Prepare a Dear Healthcare Professional letter or comparable instructive material and provide this to Medsafe for review and approval prior to distribution of this product. Due date: February 2021.

2) The New Zealand site of batch release will only release batches for distribution in New Zealand once the importer or sponsor has verified that the shipping temperature profile meets specifications.

3) Provide Certificates of Analysis to Medsafe for the first three batches of vaccine intended to be distributed in New Zealand.

4) Provide data to further characterise the truncated and modified mRNA species present in the finished product. Data are expected to cover batches used in clinical trials (for which the characterisation data could be available earlier) and the PPQ batches. These data should address results from ion pairing RP-HPLC addressing 5'cap levels and presence of the poly(A) tail. These data should also address the potential for translation into truncated S1S2 proteins/peptides or other proteins/peptides. Relevant protein/peptide characterisation data for predominant species should be provided. Any homology between translated proteins (other than the intended spike protein) and human proteins that may, due to molecular mimicry, potentially cause an autoimmune process should be evaluated. Due date: July 2021, Interim report: March 2021.

5) Provide the analysis of the main peak of the RNA integrity test representing the full-length RNA, that addresses 5'cap levels and presence of the poly (A) tail. Due date: July 2021, Interim report: March 2021.

6) Provide the reassessment of the active substance specification for the DNA template purity and impurities. Due date: July 2021.

7) Provide active substance process validation data regarding the finalised indirect filter qualification assessment and the shipping validation between sites. Due date: July 2021.

8) Comprehensively describe the capability of the next generation sequencing technology platform to detect lower amounts of RNA species of alternative sequence in the presence of the correct, more abundant RNA for the active substance. Due date: July 2021.

9) Discuss the results and the assay suitability for the cell-based flow cytometry and the western blot method used for biological characterisation of protein expression for the active substance. Due date: July 2021.

10) Provide additional data for the active substance to confirm the identities of the observed Western Blot (WB) bands obtained by the *in vitro* expression assay. Protein heterogeneity, resulting in broad bands on the WB and uncertainties in the theoretical intact molecular weight of the spike protein, is assumed to be due to glycosylation. Therefore, to further confirm protein identities, enzymatic deglycosylation of the expressed proteins followed by WB analysis should be performed. Correlation with the calculated molecular weights of the intact S1S2 protein should be demonstrated. Due date: July 2021. Interim report: March 2021.

11) Provide a summary of the validation/verification status of the immunoblot analytical procedure used to detect double stranded RNA (dsRNA) in the active substance. Due date: March 2021.

12) Reassess and revise the active substance and finished product specifications acceptance limits as further data becomes available from ongoing clinical trials and in line with manufacturing process capability and stability data of the product. Comprehensive data should be provided comprising batch analyses of a suitable number of commercial batches as well as analyses of batches that have been used in the (ongoing) clinical trials. Due date: July 2021, Interim report: March 2021.

13) Introduce an active substance specification to control Poly(A) tail length, which is considered a critical attribute and should be controlled on each batch. A suitable method should be developed and appropriate acceptance criteria should be set. Due date: July 2021, Interim report: March 2021.

14) Provide additional data to support the suitability of the method used for %poly(A) tail, or develop and introduce an alternative suitable assay. The %poly(A) tail should be characterised following any future active substance process changes. Due date: July 2021, Interim report: March 2021.

15) Revise the mRNA integrity and polydispersity finished product specifications as further data becomes available from ongoing clinical trials and in-line with manufacturing process capability. Due date: July 2021, Interim report: March 2021.

16) Provide additional data to support the suitability of the method used for potency determination or an alternative suitable assay for this purpose should be developed and introduced. Then the finished product acceptance criteria for potency should be revised accordingly. Due date: July 2021, Interim report: March 2021.

17) Lipid-related impurities should be further evaluated and an appropriate control strategy should be introduced, suitably justified and provided for assessment. Due date: July 2021, Interim report (LMS content in commercial FP batches, investigation results): March 2021.

18) Provide the summary report on the completed commercial scale process validation activities, specifically for the PPQ-batches manufactured at the Pfizer Puurs, Belgium commercial facility. Due date: March 2021.

19) Provide test results of future process validation-batches of finished product tested according to the extended comparability testing protocol. Due date: March 2021.

20) Expand the description of the finished product manufacturing process with the following details: (1) when the batch size is twice the original one, the range number of active substance bags and active substance batches to be thawed, and the number of mixers should be stated, (2) the configuration of filters used in finished product manufacture, (3) the surface area of the sterile filter should be adapted to the batch size, unless otherwise justified, (4) that process control for RNA content prior to dilution is important, particularly if several runs of TFF are performed in parallel with batch sizes. Due date: March 2021.

21) Provide data that verifies the in-process test methods used for the finished product. Due date: March 2021.

22) Provide results of the validation plan phase 2 of the rapid sterility test for assessment before implementation via a Changed Medicine Notification.

23) Provide a risk assessment with respect to the potential presence of elemental impurities in the active product based on the general principles outlined in Section 5.1 of ICH Q3D and Ph. Eur. monograph Pharmaceutical Preparations (2619). The control strategy for elemental impurities should be justified based on the risk assessment. Due date: March 2021.

24) Provide updated finished product stability data as it becomes available, including stability data for the process performance qualification batches. Due date: July 2021, Interim report: March 2021.

25) Provide a detailed summary of the ALC-0315 manufacturing process completed at the Avanti and Croda manufacturing sites. The differences in manufacture between the two sites will also be clearly detailed. Due date: July 2021, Interim report: February 2021.

26) Provide a detailed description of the ALC-0315 starting materials (including the general synthetic route), the reagents and solvents used, reaction conditions, and in-process controls. If applicable, reprocessing, reworking, and recovery/reuse operations should also be detailed. Due date: July 2021, Interim report: February 2021.

27) Provide a discussion regarding the control of the raw materials for ALC-0315. This should include the manufacture, qualified suppliers, and quality controls of the starting materials. The in-house controls applied to the raw materials and solvents used should also be detailed, as should the control of any potentially genotoxic contaminants. Due date: July 2021, Interim report: February 2021.

28) Provide information and justification on critical steps and intermediates (including specifications) for ALC-0315. Due date: July 2021, Interim report: February 2021.

29) Provide a discussion regarding process development for ALC-0315 with emphasis on the identification and purge of impurities. Due date: July 2021.

30) Notify Medsafe of any changes to the ALC-0315 manufacturing process and/or suppliers/manufacturers/testing sites using Changed Medicine Notifications.

31) Further evaluate specified impurities for ALC-0315 and include appropriate specification limits for individual impurities when more data are available. Acceptance criteria for specified and un-specified impurities should be added to the specification for ALC-0315 and should also be evaluated during stability studies. Due date: July 2021; Interim report: April 2021.

32) Update the control of the solvent residues to those that are used in the manufacture of the ALC-0315 excipient. The solvents which are not used should be removed from the specifications. Associated changes to the analytical method should be detailed and validated where necessary. Due date: July 2021.

33) Update the ALC-0315 assay and impurities limits when additional supporting data is available. Due date: July 2021.

34) Provide detailed method validation reports for assay, impurities, and residual solvents for ALC-0315. Due date: July 2021.

35) Provide ALC-0315 impurity standard information for any identified impurities reported. Due date: July 2021.

36) Provide a retest period and storage condition for ALC-0315 based on stability data. Due date: February 2021.

37) Provide updated stability data for ALC-0315 manufactured at the Avanti and Croda sites. Due date: July 2021. Interim report: April 2021.

38) Provide a detailed description of the ALC-0159 excipient manufacturing process and yields. This should include the reagents and solvents used, reaction conditions, and in-process controls. If applicable, reprocessing, reworking, and recovery/reuse operations should also be detailed. Due date: February 2021.

39) Provide information regarding the control of ALC-0159 raw materials. This should include the manufacture, qualified suppliers, and quality controls of the starting materials. The in-house controls applied to the raw materials used should also be detailed, as should the control of any potentially genotoxic contaminants. Due date: July 2021. Interim report: February 2021.

40) Provide information and justification on critical steps and intermediates (including specifications) for ALC-0159. Due date: July 2021. Interim report: February 2021.

41) Provide a discussion regarding process development for ALC-0159 with particular emphasis on identification and purge of impurities. Due date: July 2021.

42) Notify Medsafe of any changes to the ALC-0159 manufacturing process and/or suppliers/manufacturers/testing sites using Changed Medicine notifications.

43) Provide studies on the impact of the molecular weight and polydispersity of carboxy-MPEG on ALC-0159 and include acceptance criteria for these parameters in the starting material, as applicable. Due date: July 2021. Interim report: February 2021.

44) Update the control of the solvent residues to those that are used in the manufacture of the ALC-0159 excipient. The solvents which are not used should be removed from the specifications. Associated changes to the analytical method should be detailed and validated where necessary. Due date: July 2021.

45) Update the ALC-0159 assay and impurities limits when additional supporting data is available. Due date: July 2021.

46) Further evaluate specified impurities for ALC-0159 and include appropriate specification limits for individual impurities when more data are available. Acceptance criteria for specified and un-specified impurities should be added to the specification for ALC-0159 and should also be evaluated during stability studies. Due date: July 2021; Interim report: April 2021.

47) Provide detailed method validation reports for assay, impurities and residual solvents for ALC-0159. Due date: July 2021.

48) Provide impurity standard information for any identified impurities reported for ALC-0159. Due date: July 2021.

49) Provide a retest period and storage condition for ALC-0159 based on stability data. Due date: February 2021.

50) Provide updated stability data for ALC-0159. Due date: July 2021.

51) Provide regular updates on the duration of efficacy and the requirement for booster doses. This should include the six months analysis data from Study C4591001. Interim report due: April 2021.

52) Provide updates on efficacy including regarding asymptomatic infection in the vaccinated group, vaccine failure, immunogenicity, efficacy in population subgroups and results from post-marketing studies, when these become available.

53) Submit the final Clinical Study Reports for Study C4591001 and Study BNT162-01 once they become available.

54) Submit periodic safety update reports (including monthly reports) once they are available.

55) Inform Medsafe of all safety reviews they conduct or become aware of and provide the completed review.

56) Perform the required pharmacovigilance activities and interventions detailed in the agreed RMP and any agreed updates to the RMP. An RMP should be submitted at the request of Medsafe or whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important milestone being reached.

Due to the unresolved concerns and additional quality, safety and efficacy data to be provided at the time of completion of the evaluation, Medsafe is unable to recommend that this product be granted consent. It is therefore recommended that the application be referred to the Medicines Assessment Advisory Committee (MAAC) under section 22(2) of the Medicines Act 1981 for their consideration. In referring the application, it is requested that the MAAC focus on the specific aspects in their consideration of the application:

- The conditions and consent time period proposed for provisional consent under section 23 of the Medicines Act 1981. Specifically, whether these are appropriate and sufficient given the data provided up to the time of referral, as well as whether any additional conditions should be applied.

- Whether the benefit risk balance of Comirnaty vaccine for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 16 years of age and older is positive.

- Whether to accept the proposed indications, or to request that the Sponsor update the New Zealand data sheet so that it is harmonised with the TGA approved product information, and includes the following indication:

  Comirnaty (BNT162b2 (mRNA)) COVID-19 vaccine has provisional consent for the indication below:

  Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 16 years of age and older.

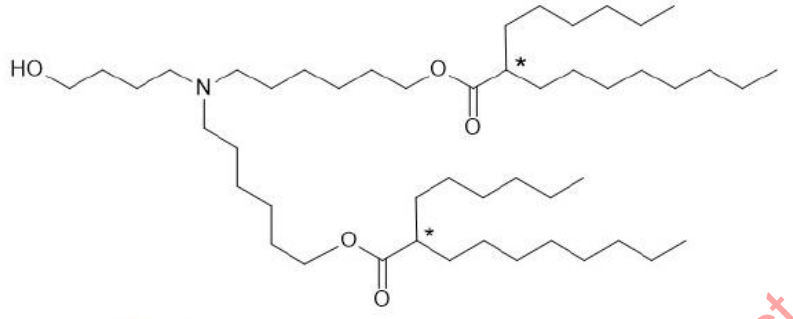
  The use of this vaccine should be in accordance with official recommendations.

  The decision has been made on the basis of short-term efficacy and safety data. Continued approval depends on the evidence of longer-term efficacy and safety from ongoing clinical trials and post-market assessment.

EVALUATION OF A NEW EXCIPIENT

Substance name: ALC-0315

Structure:



Asterisks (*) indicate chiral centers.

Molecular formula = $C_{48}H_{95}NO_5$
Molecular weight = 766.27 Da

Application ID:	109400
Applicant name and email:	s 9(2)(a) [redacted]
Associated TT50 file(s) and product names:	Comirnaty (COVID-19 mRNA vaccine) Pfizer TT50-10853
Substance form:	Colourless to pale yellow oil
Re-test period and storage conditions:	Not yet defined
Packaging:	Type III glass vials closed with PTFE liner and PP screw cap
Manufacturers and GMP:	All commercial manufacturing, testing, packaging, labelling, and release of the excipient is completed by Croda Europe Ltd., Barnfield Road, Leek, Staffordshire, ST13 5QJ, United Kingdom. Initial manufacture was completed by Avanti Polar Lipids, 700 Industrial Park Drive, Alabaster, Alabama 35007, United States.

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Module 3.2.A. ALC-0315 Excipient

3.2.A.1 General Information

The chemical being reviewed is a novel excipient proposed to be used in the Pfizer COVID-19 vaccine (TT50-10853). Due to the global pandemic, the vaccine is being marketed globally based on limited data sets with commitments to provide the missing data when this becomes available. As part of the EMA/CHMP assessment multiple post-approval commitments were made to provide the omitted data. These same commitments should be made for Medsafe. The suitability of these commitments will be reviewed as part of the MAAC assessment. The remainder of the below excipient evaluation is completed based on the assumption that the commitments will be made.

RFI1 Q.1.	***Please commit to provide Medsafe with the same additional information (specific obligations) requested by the CHMP as part of the conditional marketing authorisation in the EU for the ALC-0315 excipient.*** ***The commitments made to the EMA and FDA to review the excipient manufacturing process and quality controls should also be made to Medsafe.***
EAI1 Q.1.	*The applicant has committed to provide Medsafe with the same additional information (specific obligations) requested by the CHMP as part of the conditional marketing authorisation in the EU for the ALC-0315 excipient. In addition, the commitments made to the EMA and FDA to review the excipient manufacturing process and quality controls apply to Medsafe as well. This is acceptable.* ***Point resolved.***

3.2.A.1.1 Nomenclature

Recommended Name: ALC-0315

Avanti Product Number: 770315

Croda Europe Product Number: CM04017

Chemical Names:

• ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)

• 6-[N-6-(2-hexyldecanoyloxy)hexyl-N-(4-hydroxybutyl)amino]hexyl 2-hexyldecanoate

Chemical Abstracts Service (CAS) registry number: 2036272-55-4

3.2.A.1.2 Structure

See cover page.

This excipient contains two chiral centres, but the excipient is a 1:1 racemic mixture of the diastereomers. The excipient is not optically active.

3.2.A.1.3 General properties

ALC-0315 is a colourless to pale yellow oil which is soluble in chloroform and insoluble in water. The excipient has a specific gravity of 0.908 at 25°C and DSC results confirm the excipient is amorphous. The excipient is non-hygroscopic.

Commitments

1) The sponsor to provide a detailed summary of the ALC-0315 manufacturing process completed at the Avanti and Croda manufacturing sites. The differences in manufacture between the two sites will also be clearly detailed. Due date: July 2021. Interim report: February 2021.

2) The sponsor to provide a detailed description of the ALC-0315 starting materials (including the general synthetic route), the reagents and solvents used, reaction conditions, and in-process controls. If applicable, reprocessing, reworking, and recovery/reuse operations should also be detailed. Due date: July 2021. Interim report: February 2021.

3) The sponsor to provide a discussion regarding the control of the raw materials for ALC-0315. This should include the manufacture, qualified suppliers, and quality controls of the starting materials. The in-house controls applied to the raw materials and solvents used should also be detailed, as should the control of any potentially genotoxic contaminants. Due date: July 2021. Interim report: February 2021.

4) The sponsor to provide information and justification on critical steps and intermediates (including specifications) for ALC-0315. Due date: July 2021. Interim report: February 2021.

5) The sponsor to provide a discussion regarding process development for ALC-0315 with emphasis on the identification and purge of impurities. Due date: July 2021.

6) The sponsor will notify Medsafe of any changes to the ALC-0315 manufacturing process and/or suppliers/manufacturers/testing sites using Changed Medicine Notifications.

7) Specified impurities should be further evaluated and appropriate specification limits for individual impurities should be included when more data are available. Acceptance criteria for specified and un-specified impurities should be added to the specification for ALC-0315 and should also be evaluated during stability studies. Due date: July 2021; Interim report: April 2021

8) The sponsor should update the control of the solvent residues to those that are used in the manufacture of the ALC-0315 excipient. The solvents which are not used should be removed from the specifications. Associated changes to the analytical method should be detailed and validated where necessary. Due date: July 2021.

9) The sponsor to update the ALC-0315 assay and impurities limits when additional supporting data is available. Due date: July 2021.

10) The sponsor to provide detailed method validation reports for assay, impurities, and residual solvents for ALC-0315. Due date: July 2021

11) The sponsor to provide ALC-0315 impurity standard information for any identified impurities reported. Due date: July 2021

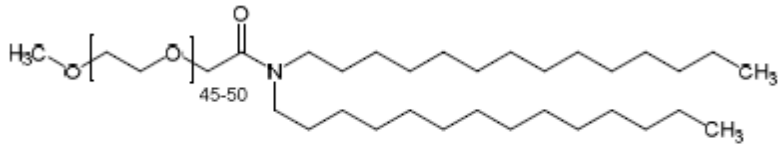
12) The sponsor to provide a retest period and storage condition for ALC-0315 based on stability data. Due date: February 2021

13) The sponsor to provide updated stability data for ALC-0315 manufactured at the Avanti and Croda sites. Due date: July 2021. Interim report: April 2021

EVALUATION OF A NEW EXCIPIENT

Excipient name: ALC-0159

Structure:



ALC-0159

Molecular formula = $(C_2H_4O)_nC_{31}H_{63}NO_2$, n=45-50
Molecular weight = 2400-2600 Da. Range is due to polydispersity of PEG polymer moiety

Application ID:	109400
Applicant name and email:	s 9(2)(a) [redacted]
Associated TT50 file(s) and product names:	Comirnaty (COVID-19 mRNA vaccine) Pfizer TT50-10853
Substance form:	White Powder
Re-test period and storage conditions:	Not yet defined
Packaging:	Type III glass vials closed with PTFE liner and PP screw cap
Manufacturers and GMP:	All manufacturing, testing, packaging, labelling, and release of the excipient is completed by: Avanti Polar Lipids, 700 Industrial Park Drive, Alabaster, Alabama 35007, United States.

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Module 3.2.A. Excipient ALC-0159

3.2.A.1 General Information

The chemical being reviewed is a novel excipient proposed to be used in the Pfizer COVID-19 vaccine (TT50-10853). Due to the global pandemic, the vaccine is being marketed globally based on limited data sets with commitments to provide the missing data when this becomes available. As part of the EMA/CHMP assessment multiple post-approval commitments were made to provide the omitted data. These same commitments should be made for Medsafe. The suitability of these commitments will be reviewed as part of the MAAC assessment. The remainder of the below excipient evaluation is completed based on the assumption that the commitments will be made.

RFI1 Q.1.	***Please commit to provide Medsafe with the same additional information (specific obligations) requested by the CHMP as part of the conditional marketing authorisation in the EU for the ALC-0159 excipient.*** ***The commitments made to the EMA and FDA to review the excipient manufacturing process and quality controls should also be made to Medsafe.***
EAI1 Q.1.	*The applicant has committed to provide Medsafe with the same additional information (specific obligations) requested by the CHMP as part of the conditional marketing authorisation in the EU for the ALC-0159 excipient. In addition, the commitments made to the EMA and FDA to review the excipient manufacturing process and quality controls apply to Medsafe as well. This is acceptable.* ***Point resolved****.*

3.2.A.1.1 Nomenclature

Recommended Name (INN): ALC-0159

Avanti Product Number: 770159

Chemical Names:

• 2-[(polyethylene glycol)-2000]-*N,N*-ditetradecylacetamide,

• 2-[2-ω-methoxy(polyethyleneglycol-2000)-ethoxy]-N-Nditetradecylacetamide, or

• Poly(oxy-1,2-ethanediyl), α-[2-(ditetradecylamino)-2-oxoethyl]-ω-methoxy-Polymer

Chemical Abstracts Service (CAS) registry number: 1849616-42-7

3.2.A.1.2 Structure

See cover page. The excipient does not have any chiral centres.

3.2.A.1.3 General properties

ALC-0159 is a white powder which exhibits a crystalline structure from its PEG moiety. The excipient is soluble in water and chloroform, has a pH of 5.99 in water, and is not hygroscopic. The polymorphic form of the excipient is not critical as this is manufactured into a lipid nanoparticle as part of the finished product manufacturing process.

[redacted]

Commitments

1) The sponsor to provide a detailed description of the ALC-0159 excipient manufacturing process and yields. This should include the reagents and solvents used, reaction conditions, and in-process controls. If applicable, reprocessing, reworking, and recovery/reuse operations should also be detailed. Due date: February 2021.

2) The sponsor to provide information regarding the control of ALC-0159 raw materials. This should include the manufacture, qualified suppliers, and quality controls of the starting materials. The in-house controls applied to the raw materials used should also be detailed, as should the control of any potentially genotoxic contaminants. Due date: July 2021. Interim report: February 2021.

3) The sponsor to provide information and justification on critical steps and intermediates (including specifications) for ALC-0159. Due date: July 2021. Interim report: February 2021.

4) The sponsor to provide a discussion regarding process development for ALC-0159 with particular emphasis on identification and purge of impurities. Due date: July 2021.

5) The sponsor will notify Medsafe of any changes to the ALC-0159 manufacturing process and/or suppliers/manufacturers/testing sites using Changed Medicine notifications

6) Specified impurities for ALC-0159 should be further evaluated and appropriate specification limits for individual impurities should be included when more data are available. Acceptance criteria for specified and un-specified impurities should be added to the specification for ALC-0159 and should also be evaluated during stability studies. Due date: July 2021; Interim report: April 2021

7) The sponsor to provide studies on the impact of the molecular weight and polydispersity of carboxy-MPEG on ALC-0159 and include acceptance criteria for these parameters in the starting material, as applicable. Due date: July 2021. Interim report: February 2021.

8) The sponsor should update the control of the solvent residues to those that are used in the manufacture of the ALC-0159 excipient. The solvents which are not used should be removed from the specifications. Associated changes to the analytical method should be detailed and validated where necessary. Due date: July 2021.

9) The sponsor to update the ALC-0159 assay and impurities limits when additional supporting data is available. Due date: July 2021.

10) The sponsor to provide detailed method validation reports for assay, impurities and residual solvents for ALC-0159. Due date: July 2021

11) The sponsor to provide impurity standard information for any identified impurities reported for ALC-0159. Due date: July 2021.

12) The sponsor to provide a retest period and storage condition for ALC-0159 based on stability data. Due date: February 2021

13) The sponsor to provide updated stability data for ALC-0159. Due date: July 2021.

CLINICAL EVALUATION

Comirnaty
(COVID-19 mRNA Vaccine)

Applicant: Pfizer/BioNTech

Based on Final Analysis Interim Report - data cutoff: 14 November 2020

TT Number	TT50-10853
Application ID	109400
Date received:	13 November 2020
Date of this report:	January 2021
Evaluator	s 9(2)(g)(ii)
Reviewer	s 9(2)(g)(ii)

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Limited glossary

ACV	TGA's Advisory Committee on Vaccines
CEF	MHC-class I restricted peptides originating from CMV, EBV, and flu (influenza) virus
CEFT	MHC-class II restricted peptides originating from CMV, EBV, Flu (influenza) virus and tetanus toxin

CoV	coronavirus
COVID-19	coronavirus disease 2019
CSR	clinical study report
EUA	(FDA's) Emergency Use Authorization
FACS	fluorescence-activated cell sorting
HCS	Convalescent human serum
IA	interim analysis
IRC	internal review committee
IRR	illness rate ratio
IWR	interactive Web-based response
LNP	lipid nanoparticle
MERS	Middle East respiratory syndrome
modRNA	nucleoside-modified messenger ribonucleic acid
NAAT	nucleic acid amplification test
N-binding	SARS-CoV-2 nucleoprotein binding
NT50	neutralizing titer 50
NT90	neutralizing titer 90
NVA	nonvaccine antigen
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
P/B	Dose 1/Dose 2: a dosing regimen, comprising a priming immunization (dose 1) and a dose 2 immunization (dose 2)
PBMCs	peripheral blood mononuclear cells
RBD	receptor-binding domain
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SIRVA	shoulder injury related to vaccine administration
SRC	Safety Review Committee
Tdap	diphtheria vaccine toxoid; pertussis vaccine acellular 3 component; tetanus vaccine toxoid

SUMMARY REPORT

I. INTRODUCTION

Pfizer have submitted a new medicine application, received 13 November 2021 (ID 109400), for a nucleoside modified messenger RNA (modRNA) vaccine: the Pfizer-BioNTech COVID-19 Vaccine (BNT162b2 30 µg): Comirnaty (COVID-19 mRNA Vaccine).

Comirnaty (30 μg), is administered intramuscularly (IM) as a series of two 30-μg doses of the diluted vaccine solution (0.3 mL each) according to the following schedule: a single dose followed by a second dose 21 days later.

The proposed indication is as follows.

> COMIRNATY is indicated for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 16 years of age and older.
>
> The use of this vaccine should be in accordance with official recommendations.
>
> *Evaluator's comment*
>
> *The TGA's Delegate's Overview shows that the 'Indication revised by Sponsor following TGA request' is as follows:*
>
> > COMIRNATY (BNT162b2[mRNA]) COVID-19 Vaccine has **provisional approval** for the indication below:
> > Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 16 years of age and older.
> > The use of this vaccine should be in accordance with official recommendations.
> >
> > The decision has been made on the basis of short term efficacy and safety data. Continued approval depends on the evidence of longer term efficacy and safety from ongoing clinical trials and post-market assessment.

This vaccine encodes P2 S (V9), expresses a prefusion stabilized full-length variant of the SARS-CoV-2 S-glycoprotein.

The RNA-based vaccine is formulated in lipid nanoparticles (LNPs) and includes two novel lipid excipients.

Proprietary Name of Drug Product	To be determined
Non-proprietary or Common Name of Drug Product	COVID-19 Vaccine
Compound Name	BioNTech code number BNT162b2
Dosage Form(s)	Liquid Concentrated Formulation in a 2 mL vial
Strength(s)	225 μg/vial
Route of Administration	Intramuscular injection

Formulation

The vaccine candidate will be released as a concentrated multi-dose liquid formulation stored frozen at -90 to -60 °C in a 2 mL Type 1 glass vial to be thawed and subsequently diluted with sterile 0.9% sodium chloride Solution for Injection, USP (saline diluent), and stored at 2-8 °C until administration.

Dose and administration

The vaccine will be administered intramuscularly (IM) in the upper arm (deltoid muscle) as a series of two 30 μg doses of the diluted vaccine solution (0.3 mL each) according to the following schedule: a single 0.3 mL dose followed by a second 0.3 mL dose 21 days later (prime/boost regimen).

The draft datasheet includes, among other details, that the vaccine comes as concentrated suspension for injection for 5 doses in a 2 mL clear vial.

Store in a freezer at -90 °C to -60 °C. After thawing, the vaccine should be diluted and used immediately. After dilution, store the vaccine at 2 °C to 30 °C and use within 6 hours.

Evaluator's comment

The above instructions, and details from the datasheet, will be compared against those in the IP manual when this becomes available.

Data cutoff

This report is regarding the final analysis interim report - 14 November 2020 data cutoff [the 2,033 page report is dated "04-Dec-2020" in the margin]. This is the same data cutoff as data found in Emergency Use Authorization (EUA) report.

s 9(2)(b)(ii) [redacted]

s 9(2)(b)(ii)

[redacted]

s 9(2)(b)(ii)

IV.5 Evaluator's overall conclusions on clinical efficacy

With currently available data from the pivotal study, follow-up data is only available for about one to two months. Therefore there is uncertainty about how long protection will last. In addition, the number of cases of symptomatic COVID-19 in subgroups of the study population is often low. There is thus uncertainty regarding efficacy in people of Polynesian and Asian ethnicity.

The pivotal study for this application is the Phase 2/3 Study C4591001 is ongoing in the USA, Argentina, Brazil, Germany, South Africa, and Turkey with the first subject first visit on 29 April 2020.

Study participants had median age 52 ears, with about 22% 65 years of age or older. There were 76 participants (0.2%) of Native Hawaiian or other Pacific Islander ethnicity. There were 1,625 participants of Asian ethnicity. At baseline, about 21% of participants had any Charlson comorbidity (including diabetes 8% and chronic pulmonary disease 8%). At baseline, 197 subjects (0.5%) had HIV infection.

The pivotal study shows two doses the modRNA COVID-19 Vaccine (BNT162b2 30 µg) three weeks apart provide 95% protection against symptomatic COVID-19 (as at data cutoff 14 November 2020, n≈ 37,000 with follow-up usually about one to two months).

At the earliest, it is from April 2021 that updated efficacy estimates regarding longer duration of vaccine protection are expected to become available.

For participants without evidence of SARS-CoV-2 infection before and during vaccination regimen, from 7 days after the second dose, there were the following cases of symptomatic laboratory-confirmed COVID-19 of any severity;

- 8 (out of 18,198; 0.04%) in the BNT162b2 group and
- 162 (out of 18,325; 0.9%) in the placebo group.

In the placebo group, 162 instances of symptomatic COVID infection in about 2,222 person-years. Given the approximately 18,000 subjects who received placebo, surveillance time for the majority of subjects is likely to be between one to two months.

For the other co-primary efficacy endpoint, VE against confirmed COVID-19 in participants with or without evidence of SARS-CoV-2 infection was 94.6% (with 9 and 169 cases in the BNT162b2 and placebo groups respectively). In the elderly, participants ≥65 years of age with or without prior evidence of SARS-CoV-2 infection, VE was 94.7% (corresponding to 1 case in the BNT162b2 and 19 in the placebo groups).

'Severe' confirmed COVID-19 meant that subject had in addition to the confirmed Covid-19 (for example) at least; severe systemic illness (eg RR ≥30 breaths per minute); or needing high-flow oxygen, or admission to an ICU; or death. Severe disease was noted in one case of the vaccinated group and 3 cases in the placebo group. Although at this stage of the study's follow-up, only about 1% of placebo subjects have developed symptomatic COVID-19, severe disease was not common (about 2% of those with symptomatic disease had severe disease; 3 out of 162).

Some subjects who at baseline had evidence of prior COVID-19 infection, subsequently developed symptomatic COVID-19 at least 7 days after Dose 2. As noted in the VRBPAC Briefing Document, only 3% of participants had evidence of prior infection at study enrolment. These data do suggest that previously infected individuals can be at risk of COVID-19 (i.e., reinfection) and could benefit from vaccination.

V. s 9(2)(b)(ii)

s 9(2)(b)(ii)

Pages 49- 69 withheld under section 9(2)(b)(ii) of the Act.

s 9(2)(b)(ii) [redacted]

V.8 Post marketing experience/Norway deaths

There are reports of deaths of 23 frail elderly patients shortly after receiving the Pfizer BioNTec vaccine. The Norwegian Medicines Agency (NOMA) has commented that there is no certain connection between these deaths and the vaccine.

The agency has investigated 13 of the deaths so far and concluded that common adverse reactions of mRNA vaccines, such as fever, nausea, and diarrhoea, may have contributed to fatal outcomes in some of the frail patients. "There is a possibility that these common adverse reactions, that are not dangerous in fitter, younger patients and are not unusual with vaccines, may aggravate underlying disease in the elderly".

Norwegian Authorities have prioritized the immunization of residents in Nursing Homes, most of whom are very elderly with underlying medical conditions and some which are terminally ill. NOMA confirms the number of incidents so far is not alarming, and in line with expectations.

All reported deaths will be thoroughly evaluated by NOMA to determine if these incidents are related to the vaccine. The Norwegian government will also consider adjusting their vaccination instructions to take the patients' health into more consideration.

https://www.bmj.com/content/372/bmj.n149

News. Covid-19: Norway investigates 23 deaths in frail elderly patients after vaccination

BMJ 2021; 372 doi: https://doi.org/10.1136/bmj.n149 (Published 15 January 2021)Cite this as: BMJ 2021;372:n149

V.9 Evaluator's overall conclusions on clinical safety

In the Phase 2/3 Study C4591001 subjects were randomised to receive the modRNA COVID-19 Vaccine (BNT162b2 30 µg) three weeks apart. As at data cutoff 14 November 2020, safety information is available for the all subjects' safety population N~38,000 with medium follow-up of two months. The safety population with at least 2 months of follow-up after dose 2 had n = 19,067.

The vaccine is reactogenic, which is evident especially through information from the Phase 2/3 reactogenicity subset (using e-diary reporting). As per the CHMP assessment report summary: "Regarding reactogenicity, the most frequent adverse reactions in participants 16 years of age and older were injection site pain (> 80%), fatigue (> 60%), headache (> 50%), myalgia and chills (> 30%), arthralgia (> 20%), pyrexia and injection site swelling (> 10%). All reactions were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age. The frequency of headache, fatigue and fever was higher after Dose 2 in both age groups."

For participants who were not in the reactogenicity subset, local reactions and systemic events consistent with reactogenicity were detected and reported as AEs. AEs judged to be related to vaccination were noted in 21% of BNT162b recipients vs 5% in the placebo group. This includes injection site pain (7%), pyrexia (4%), as well as chills, fatigue, headache, and myalgia at lesser levels.

AEs were usually reported at a higher level in the younger (18-55 Years of Age) age group than in the older (65-85 Years of Age) age group. For example, 31% of this younger age group had moderate pain after the first dose, and 27% after the second dose. Systemic symptoms were common especially following the second dose (eg fatigue, headache, muscle pain and joint pain). Fever of ≥38.0° C after the second dose was noted in the younger group by 15.8%, and of ≥38.0° C to 38.4° C by 9.2%.

However, severe AEs were reported in 1.2% of the vaccine group compared to 0.6% of the (saline) placebo group, and AEs leading to withdrawal 0.2% vs 0.1%.

Uncommonly reported was lymphadenopathy in the arm and neck region (0.5% in the younger group). This was reported within 2 to 4 days after vaccination, and sometimes was slow to resolve. In addition, one subject reported angioedema 13 days after Dose 1 affecting both eyes, and another subject report hypersensitivity (allergy attack).

There was an imbalance of cases of Bell's palsy (4 in the vaccine group and none in the placebo group).

VI. BENEFIT RISK ASSESSMENT

Covid-19 pandemic

In early 2021 it is becoming clear that the novel coronavirus SARS-CoV-2 constitutes an important health hazard, especially for the elderly as well as people with comorbidities. Even relatively low mortality rates associated with the resulting disease, COVID-19, may have a substantial impact as the whole population is assumed to be susceptibility. There have now been months of waves of increased transmission and disease. In addition to the immediate sickness, a relevant proportion of patients suffer longer term adverse consequences; including eg respiratory and cardiovascular system impairment, as well as long-Covid syndrome.

Medical need

Public health measures have been shown to be potentially very effective, although such measures can be socially disruptive and can have large economic consequences.

Treatment of acute Covid-19 disease has improved, and several medicines are recognised to have a role in treatment.

Populations for benefit risk assessment

The probability of exposure to the virus, as well as the mortality and morbidity burden associated with the disease is relevant to the benefit risk. Arguably, the following populations could be considered for separate benefit risk assessments.

- The benefit risk balance of a COVID-19 Vaccine as a travel vaccine for the elderly would likely be positive for many vaccines with reasonable efficacy and safety, as globally the virus is now endemic and chance of exposure is high.
- For New Zealand residents, staff at quarantine facilities, as well as Air New Zealand staff working on international routes and healthcare professionals, are at increased risk of contact with the virus.
- As long as public health measures continue to be effective, vaccination of New Zealanders generally could become relevant when vaccine supplies allow for the entire New Zealand resident high-risk population to be covered.

Vaccine characteristics

The vaccine's preservative free multiple dose presentation, with need for administration close to low-temperature storage, will likely result in use in group-settings rather than episodic individual use setting (such as relevant for a travel-vaccine). Given the LNP-mRNA vaccine innovative technology, particular care in the evaluation of safety (including longer-term safety) is important.

Benefit

The randomised Phase 2/3 Study C4591001 shows that for participants without evidence of SARS-CoV-2 infection before and during vaccination regimen, from 7 days after the second dose, there were the following cases of symptomatic laboratory-confirmed COVID-19 of any severity:

- 8 (out of 18,198; 0.04%) in the BNT162b2 group and
- 162 (out of 18,325; 0.9%) in the placebo group.

With currently available data from the pivotal study, follow-up data is only available for about one to two months. Therefore there is uncertainty about how long protection will last. At the earliest, updated efficacy estimates regarding longer duration of vaccine protection are expected to become available from April 2021.

In addition, the number of cases of symptomatic COVID-19 in subgroups of the study population is often low. There is thus uncertainty regarding efficacy in people of Polynesian and Asian ethnicity.

Severe disease was noted in one case of the vaccinated group and 3 cases in the placebo group; an estimated efficacy against severe COVID-19 occurring at least 7 days after dose 2 was 66.4% (95% CI: -124.8%; 96.3%).

Risk

The vaccine is reactogenic, which is shown especially through information from the Phase 2/3 reactogenicity subset (using e-diary reporting), for example: injection site pain (> 80%), myalgia and chills (> 30%), and pyrexia and injection site swelling (> 10%) are very common. There are lesser rates when reporting of AEs is considered, for example general disorders and administration site conditions (12% BNT162b2 vs 3% placebo). In general, AEs judged to be related to vaccination were noted in 21% of BNT162b recipients vs 5% in the placebo group - AEs includes injection site pain (7%), pyrexia (4%), as well as chills, fatigue, headache, and myalgia at lesser levels. Severe AEs were reported in 1.2% of the vaccine group compared to 0.6% of the (saline) placebo group, and AEs leading to withdrawal 0.2% vs 0.1%. Longer-term safety data is lacking.

AEs were usually reported at a higher level in the younger (18-55 Years of Age) age group than in the older (65-85 Years of Age) age group. For example, 31% of this younger age group had moderate pain after the first dose, and 27% after the second dose. Systemic symptoms were common especially following the second dose. Fever of ≥38.0° C after the second dose was noted by about 16% in the younger group.

Uncertainties

Pivotal trial design and sample size means that study results are not expected to address all of the following uncertainties.

- It is not clear that the method of administration of the Comirnaty vaccine, as described in the datasheet's 'Special precautions for disposal and other handling' section, is similar to the method of administration in the pivotal study.
- The duration of vaccine protection has not been established beyond two months.
- At this stage, there is limited evidence of protection against severe disease.

- There is no long-term safety follow-up information.
- Vaccine prevention of asymptomatic infection and disease transmission has not been established.

At this stage there is no information regarding vaccine effectiveness regarding:

- new variant virus lineages that may become important epidemiologically (including the possibility of change because of vaccine-selection pressures)
- immunocompromised people, and for pregnant women
- Pacific and Asian populations
- subjects with evidence of prior COVID-19 infection at baseline.

Summary

The benefit risk balance of Comirnaty (COVID-19 mRNA Vaccine) for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 16 years of age and older, is not clear. At this stage, there is evidence only for short-term protection, and longer-term safety data are lacking. However, experience with the vaccine is accumulating rapidly.

Notwithstanding uncertainties, in the light of high clinical need and the expectation of further data (including regarding duration of protection) around April 2021, a provisional consent under section 23 of the Medicines Act 1981 may be appropriate.

VII. PRODUCT INFORMATION

If considered for provisional consent, the datasheet will have to explain that approval was based on short-term vaccine-protection information, and that further information is expected.

Among others, issues covered in the datasheet include the following.

The study programme did not cover pregnant women and children.

Pregnancy

There is limited experience with use of COMIRNATY in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition or post-natal development (see Section 5.3 Preclinical safety data).

Administration of COMIRNATY in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus.

Evaluator's comment

s 6(b)(ii) [redacted] *It is often advantageous for the New Zealand datasheet to be similar to the information for prescribers in Australia, and updating the pregnancy information in the proposed New Zealand datasheet to be similar to that for Australia should be considered.*

IM administration

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, COMIRNATY should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any

coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Hypersensitivity

4.4 Special warnings and precautions for use

General recommendations

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of COMIRNATY.

Close observation for at least 15 minutes is recommended following vaccination. A second dose of COMIRNATY should not be given to those who have experienced anaphylaxis to the first dose of COMIRNATY.

Evaluator's comment

For justification of the above general recommendation, see the section in the Safety part of this report regarding the MHRA notification of two allergic reaction events in UK December 2020.

VIII. RECOMMENDATION

The application is to be referred to the MAAC for final recommendation on provisional consent, as well as the proposed conditions.

IX. SELECTED INITIAL ADVISORY GROUP COMMENTS

Responses to an early request (with very limited information) for advice from the Medsafe COVID-19 Vaccine Advisory Committee have included the following.

Covid-19 vaccines can be expected not to provide long term protection – the need for booster doses can be expected. (For viral vectored vaccines, heterologous boosting may be needed).

Significant delayed adverse consequences of vaccination, generally, are very uncommon. For example, a recent article highlighted vaccines that had been withdrawn for safety concerns. All of the events, resulting in withdrawal, occurred within 2 months of vaccine receipt (Reid S Vaccine Safety NZMJ 21 February 2020 Vol 133 No 1510. www.nzma.org.nz/journal-articles/vaccine-safety). Possible delayed AEs could include:

- VAERD in specific age groups (eg geriatric, pediatric) or in individuals with uncommon comorbidities (eg autoimmunity / immune deficiency)
- Guillain Barre Syndrome
- narcolepsy.

s 9(2)(b)(ii)

[redacted]

Pages 75- 77 withheld under section 9(2)(b)(ii) of the Act.

s 9(2)(b)(ii)

[redacted]

II. SUMMARY

Comirnaty COVID-19 mRNA vaccine

This application concerns the Pfizer-BioNTech nucleoside modified messenger RNA vaccine, Comirnaty COVID-19 mRNA vaccine that is administered as two intramuscularly injected doses, 21 days apart. This innovative lipid nanoparticle RNA-based vaccine includes two novel lipid excipients. Administration is made more challenging by its availability as a concentrated multi-dose liquid formulation stored frozen at -90 to -60 ° C.

Analysis of condition and current treatment options

Although treatments have improved, COVID-19 causes substantial morbidity and mortality in a susceptible population. Vaccination can mitigate the impact of COVID-19.

Benefits

The pivotal study shows two doses the Comirnaty COVID-19 mRNA vaccine (BNT162b2 30 µg) three weeks apart to provide a high level (95%) of protection against symptomatic COVID-19 (as at data cutoff 14 November 2020, n≈ 37,000 with follow-up usually about one to two months).

Uncertainty

There is uncertainty regarding the duration of protection. In addition, it is not known whether vaccinated people can become infected asymptomatically and whether they can transmit the virus. At this stage, it is not known whether the vaccine protects against severe disease, and whether it would provide protection for subgroups (such as, for example, the elderly).

The Sponsor, in response to the Request for Information, noted that efficacy data is expected in 2021.

- Q1 2021; initial results regarding the possibility of asymptomatic infection in the vaccinated group.
- First half of 2021; Information regarding vaccine failure in patients given 2 doses of vaccine.
- Q3 2021; immunogenicity data for a subset of participants.
- Q3-4 2021; information regarding duration of vaccine protection.

If considered for provisional consent, the datasheet could (as is not uncommon) harmonise with the TGA approved product information and have an indication that explains that approval was based on short-term vaccine-protection information, and that further information is expected.

Risks

In the study programme, safety of the Comirnaty COVID-19 mRNA vaccine was similar to that of IM administered vaccines.

Uncertainty

While there is uncertainty regarding the unlikely possibility of rare or delayed AEs, there is increasing assurance of the safety of the Comirnaty COVID-19 mRNA vaccine with rapidly increasing international experience. Monthly periodic safety update reports will be expected for the first 6 months post approval.

II.1 Advice sought

In its consideration of this application, the Medicines Assessment Advisory Committee (MAAC) is asked to advise whether:

– The proposed conditions for the provisional consent are appropriate.

- The benefit risk balance of the Comirnaty COVID-19 mRNA vaccine for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 16 years of age and older is positive.
- Whether to accept the proposed indications, or to request that the Sponsor update the New Zealand datasheet so that it is harmonised with the TGA approved product information, and includes the following indication:

  Comirnaty (BNT162b2 (mRNA)) COVID-19 vaccine has **provisional consent** for the indication below:

  Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 16 years of age and older.

  The use of this vaccine should be in accordance with official recommendations.

  The decision has been made on the basis of short-term efficacy and safety data. Continued approval depends on the evidence of longer-term efficacy and safety from ongoing clinical trials and post-market assessment.

II.2 Proposed conditions of provisional consent

- The sponsor must provide regular updates on the duration of efficacy and the requirement for booster doses. This should include the six months analysis data from Study C4591001. Interim report due: April 2021.
- The sponsor must provide updates on efficacy including regarding asymptomatic infection in the vaccinated group, vaccine failure, immunogenicity, efficacy in population subgroups and results from post-marketing studies, when these become available.
- The sponsor must submit the final Clinical Study Reports for Study C4591001 and Study BNT162-01. Due date: December 2023.
- (Monthly safety updates for the first six months following approval are covered through the RMP.)

Document 11

SCIENCE & TECHNICAL ADVISORY | RŌPŪ TOHUTOHU I TE PŪTAIAO ME TE HANGARAU

MINISTRY OF HEALTH
MANATŪ HAUORA

Request for Information (RfI)

This form contains the details relevant to the questions posed to the Science and Technical Advisory (STA) team. The STA will respond to the request using this form which will also be stored in the STA content management system for future reference.

This form, or parts of it, may also be forwarded to other relevant parties as appropriate.

Title	Implications of UK variant for vaccine assessment		
Subject	Summary – evidence of increased transmissibility of UK variant		
Reference No.	133	Date Received	15/01/2021
Requestor	Chris James (Medsafe), s 9(2)(g)(ii) [redacted]	Date Due	20/01/2021
Advisor	s 9(2)(g)(ii) [redacted]	Date Completed	20/01/2021
Reviewed by	s 9(2)(g)(ii) [redacted]		
Information issued to			
Approved by			
Deliverables	Evidence summary		
Request Outline	**Background/Context** Chris James from Medsafe has been informed of an increasing risk of COVID community spread since before Christmas due to new variants, and that there has been an increase in transmission in other countries due to new variants. There are concerns over what this means for New Zealand. The evidence of increased transmissibility needs to be documented, as this helps Medsafe with benefit risk consideration of the vaccine – i.e. has the benefit risk consideration changed, and is a decision based on earlier data justified? Recommendations for vaccine roll out etc are not required, and it doesn't need to be a comprehensive literature search. **Questions** What is the evidence that new variants of concern, such as the UK variant, have increased transmissibility? **Intended application of advice** This advice will accompany Medsafe's assessment report that will go to the Medicines Assessment Advisory Committee.		

Timeline

Timeframes are extremely tight. Hence Medsafe needs this by 20 January. A delay may result in a delay on regulatory decision making as this advice will accompany the assessment report that will go to the Medicines Assessment Advisory Committee.

Evidence summary: transmissibility of SARS-CoV-2, particularly new Variants of Concern (VOC)

Introduction

All viruses constantly change through mutation, and therefore the emergence of new variants is expected (1). Some mutations do not confer a direct benefit to the virus, some may be detrimental, and some may confer an advantage (2). New variants may emerge and disappear, or they may persist (3). Most mutations won't significantly impact viral spread, but some mutations or combinations of mutations may give viruses a selective advantage (e.g. increased transmissibility due to an increase in receptor binding, or evasion of the host immune response by altering viral surface structures)(1). Many thousands of variants of SARS-CoV-2 are circulating, and most will likely have no effect on viral transmission or disease characteristics (1). Variants with potential to increase the risk to human health are considered variants of concern (VOC)(1).

Multiple variants of SARS-CoV-2 have been documented globally throughout the course of the pandemic (3), but some recent variants are causing particular alarm because of reported increases in transmissibility. Three variants of note are discussed in this paper, which appear to have emerged in the UK (lineage B.1.1.7), South Africa (501.V2) and Brazil (P.1). Lineage B.1.1.7 (UK variant) is discussed in most detail as it has more information available. Scientists are working to figure out whether new variants such as these may transmit more easily, cause more severe disease, or affect the efficacy of therapeutics or vaccines (3). Epidemiologically, it is quite difficult to distinguish contributors to more efficient spread (e.g. human behavioural factors, vs virologic factors)(4).

This evidence summary provides background information about the transmissibility of SARS-CoV-2 in general, and the UK variant in particular. It also considers potential implications.

A note on naming conventions: When a number of mutations occur together and become commonly detected, they are designated as a lineage or variant. A viral strain is typically a substantial change in the virus – the consensus is that none of the SARS-CoV-2 lineages are yet at a point where they are designated as a formal strain.

UK variant

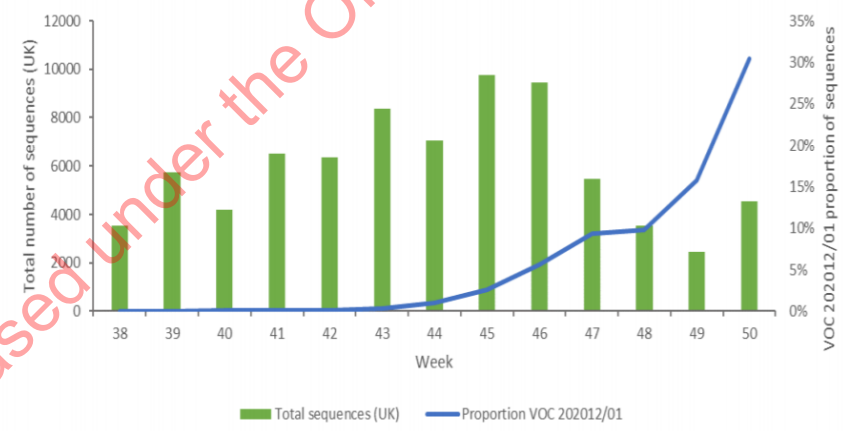
Origin, discovery and spread

- In December 2020, a new variant of SARS-CoV-2 (called VOC-202012/01) was reported in the United Kingdom (5). It was designated a Variant Under Investigation on detection and re-designated as a Variant of Concern (VOC) on 18 December 2020 (6). It is also called lineage B.1.1.7. This variant was identified by the COVID-19 Genomics UK (COG-UK) consortium, which undertakes random genetic sequencing of positive samples from around the UK to help track outbreaks and identify variants (7). The authors of the COG-UK report hypothesise that the accelerated mutation accumulation in this lineage may have resulted, at least partly, from virus evolution within a chronically infected individual

(8). However, they are careful to note we cannot yet know precisely what gave rise to this lineage. Experts indicate it is likely to have evolved in the UK (7).

- The first COVID-19 case with the VOC 202012/01 variant in England was detected on 20 September 2020. Throughout December 2020, a cluster of the new variant grew rapidly, and spread to other UK locations (8). The UK experienced a rapid increase in COVID-19 case rates (with the seven-day case rate increasing from 162 cases/ 100,000 population in week 49/2020, to 344 during week 51/2020 (1). This increased case rate was especially significant in London, the South East and the East of England, and genomic analysis identified that a large proportion of sequenced cases in these areas were a new variant, VOC 202012/01 (1). The rapid increase in COVID-19 cases overall was noted to be temporally associated with the emergence of a new variant in the abovementioned areas in November 2020 (1). The B.1.1.7 lineage rapidly emerged to become the dominant SARS-CoV-2 variant circulating in England (6).
- In response to the increase in VOC 202012/01, in late December the UK announced stricter control measures to be applied, especially in affected areas in England (1)
- As of 13 December 2020, VOC 202012/02 had been identified in 1108 individuals in the UK, in nearly 60 different local authorities (7). The figure below from the ECDC risk assessment displays how the overall proportion of VOC202012/01 among all uploaded viral sequences from the UK to the GISAID database increased substantially towards the end of 2020. However, it should be noted that this data is derived from community-based sampling, and is not geographically representative, or representative of hospitalised cases (1).

Figure 5. Fraction of UK SARS-CoV-2 sequences classified as VOC 202012/01 per week, and total sequences per week from the UK, published in GISAID EpiCoV up to 27 December 2020



Source: GISAID EpiCov database. Weeks 51 and 52 are omitted due to very few sequences being available for those weeks (252 and 0 respectively).

- As of 4 January 2021, a total of 6,008 cases with this variant had been identified in England, via routine genomic surveillance, across the majority of local authorities (7). Most cases were identified in London and the East and South East of England but the variant has also been reported elsewhere, including Wales and Scotland (7).
- As of 7th Jan 2021, 45 countries had reported the presence of the B.1.1.7 variant (5), including in managed isolation in New Zealand. As of 18 January, 16 cases of the B.1.1.7 variant were reported in New Zealand.

- The B.1.1.7 variant is quickly becoming the dominant lineage across the UK, though it is unclear how much this is due to viral genetics, versus seasonal changes and social factors. As of 4 January 2021, the new variant comprises approximately 71.5% of new cases in the UK. However, the new variant may not be simply replacing the current strain, but also adding to existing variant: "Further, excess SGTF growth rates generally outweighed declines in non-SGTF positives, showing B.1.1.7/VOC202012/01 is likely adding to, rather than replacing, existing strains". (9)

UK variant features

- The B.1.1.7 variant is characterised by a set of 17 mutations present across several genes (2). Many of these mutations have been identified before in varying frequencies (2), but the large number and combination of these in a variant is new (8). Several of the genetic changes occur in the spike protein (4)(8), which the virus uses to enter host cells.
- Three key genetic changes to the spike protein include a mutation at position 501, a deletion at position 69-70, and P681H. The mutation N501Y is in the receptor binding domain of the spike protein. This may be particularly significant because theoretically, changes in this part of the spike protein may make the virus more easily transmissible (7). N501Y has been associated with increased infectivity and virulence in a mouse model (4). This mutation has also been reported in South Africa, Australia, Denmark, Brazil and the US (2). H69del/V70del may be associated with immune response evasion (9). The spike protein deletion at position 69-70 also affects PCR assays targeting the S-gene by preventing probe binding and causing S-gene target failure (SGTF)(1, 9). SGTF can be used as a proxy to screen for VOC 202012/01, though whole genome sequencing is more definitive.

Transmissibility of the UK variant

- Preliminary analysis in the UK indicated that this variant is significantly more transmissible than other variants – it may increase transmissibility up to 30-50%, and increase the reproductive number by 0.4 (10). (6).
- The proportion of cases tested which have the proxy S gene target failure (SGTF) – a proxy target that can be reliably used to identify VOC 202012/01 - continued to rise through December in England. In the first week of December approximately 27.7% of cases contained SGTF, rising to 71.5% in the week 29 December 2020 to 4 January 2021 (6).
- The 'secondary attack rate' (SAR) is the percentage of contacts of a case who become infected. A secondary attack analysis by Public Health England estimated that 14.7% of the contacts of a case with VOC 202012/01 become infected, compared to 11% of contacts of a wild type case (6). However, the study did not cite whether these were close or causal contacts, and it is unclear what biases may affect this data (e.g. focusing testing on areas where B.1.1.7 is common will result in higher proportions of tests with that variant).
- Other countries that prioritise genome sequencing, notably Denmark, have also seen a rapid rise in the proportion of B.1.1.7 variants in their sequencing data, which increases confidence that the lineage is in fact more transmissible, rather than it becoming more common in the UK due to other factors.
- A pre-print posted by Volz et al on 4 January examined epidemiological evidence for the lineage B.1.1.7 having a transmission advantage, through several analyses (11). All indicated that this VOC has a substantial transmission advantage. The key metric is that the R_o (reproduction number) of this

VOC was 0.4-0.7 higher than previously circulating variants, which is a significant shift. The ratio of reproduction numbers varied between 1.4 and 1.8.

Volz et al also note a small but statistically significant shift towards higher rates of infection by the VOC in those under 20, compared to non VOC. However, it is possible that this is related to movement/ mixing of this cohort, rather than viral genetics.

- A pre-print posted on 27 December 2020 reported that individuals with B.1.1.7 had higher viral loads (which may result in more viral shedding from infected individuals, and may translate to higher infective doses)(4).
- Another pre-print from 15 January 20201 concluded that "direct population-representative estimates show that the B.1.1.7/VOC202012/01 SARS-CoV-2 variant leads to higher infection rates, but does not seem particularly adapted to any age group"; there was no evidence that the rates of the new variant were growing faster or slower in those under and over high school age. (9)
- Some countries have reported increases in the relative frequency of B.1.1.7, but several factors may affect reporting estimates (5). O'Toole et al (2021) note that the number of variant genome sequences reported in each countries will be influenced by the amount of local genomic surveillance, potential targeting of sequencing towards travellers from certain countries, the amount of international travel among affected countries, and the amount of local transmission (5)

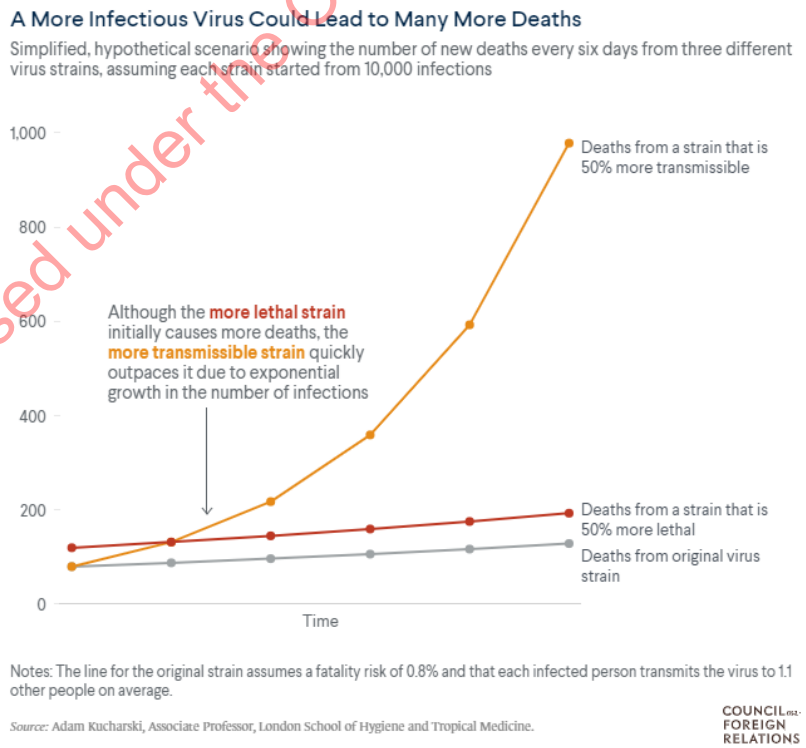
Other variants

- On 18 December 2020, the South African government reported the emergence and rapid increase of another new variant identified through routine genomic surveillance, designated 501.V2(1). This variant also has multiple changes in the spike protein, including the same N501Y mutation present in VOC 202012/01. The South African variant (also known as 20H/501Y.V2 or B.1.351) appears to be more transmissible(12); One preprint estimates that the South African variant is 50% more transmissible than previous variants(13) similar to the increased transmissibility of the UK variant.
- The South African variant contains multiple mutations affecting the spike protein, including K417T, E484K, N501Y. One of the mutations, E484K, has the potential to reduce antibody recognition, and it may help SARS-CoV-2 to bypass immune protection provided by prior infection or vaccination.(14) As of 7 January 2021, 13 countries had reported B.1.351/501Y.V2 (5).
- In a preliminary study evaluating the effectiveness of the Pfizer/BioNTech vaccine against the N501Y mutation, found in both the UK and South African variants, researchers found no reduction in neutralizing activity against the virus with the N501Y mutation (15). However, this study did not evaluate the full set of observed spike mutations.
- A Brazilian variant (known as P.1 lineage or 20J/501Y.V3) also has multiple mutations affecting the spike protein and shares the same K417T, E484K, and N501Y spike protein mutations as the South African variant. There is evidence to suggest that some of the mutations in the P.1 variant may affect its transmissibility and antigenic profile, which may affect the ability of antibodies generated through a previous natural infection or through vaccination to recognize and neutralize the virus (16).
- A recent study reported on a cluster of cases in Manaus, the largest city in the Amazon region, in which the P.1 variant was identified in 42% of the specimens sequenced from late December. In this

region, it is estimated that approximately 75% of the population had been infected with SARS-CoV2 as of October 2020. However, since mid-December the region has observed a surge in cases. The emergence of this variant raises concerns of a potential increase in transmissibility or propensity for SARS-CoV-2 re-infection of individuals(17).

Implications of new variants

- New variants such as the B.1.1.7 lineage are having significant implications for managing the COVID-19 pandemic world-wide, for example with increased travel bans internationally, and more elaborate testing regimens.
- The increased transmissibility would likely lead to greater number of secondary cases and hence increase the burden on contact tracing; As preliminary data suggests, the number of contacts infected is 50% higher compared to the current strain (e.g., if the index case has 100 contacts, number infected increases from, say, 12 previously to 18 with new variant).
- While there is no evidence that the UK VOC is responsible for more severe disease, the fact that it infects more people may result in a higher number of people that need medical care. This is observed in both the test positivity rates and the hospitalisation numbers out of the UK. A 'back of the envelope' calculation (below) from a mathematical epidemiologist at the London School of Hygiene and Tropical Medicine, shows that, compared to a virus that infects 10% of contacts with an 0.8% mortality rate, a variant that is 50% more transmissible leads to an increased number of daily deaths(18). Note that this is a very simple analysis for a media brief, comparing hypothetical exponential growth curves and does not take into account any other factors related to transmissibility.



- The CDC has noted that modelling suggests that lineage B.1.1.7 has the potential to increase the U.S. pandemic trajectory, warranting universal and increased compliance with mitigation strategies and suggesting that higher vaccination coverage might be needed to protect the public, i.e., the herd

immunity threshold is greater but there is no difference in the individual protection afforded by the vaccine. The CDC predicts that B.1.1.7 may well become the dominant variant in the US by April-May 2021(19).

Conclusions

- It seems likely that the UK variant B.1.1.7 has significantly increased transmissibility. The latest evidence from Public Health England using contact tracing data, estimates that the new variant increases the number of infected contacts of the index case by 30-50%, and this is seen consistently across geographic regions in England.
- This coupled with the high rates of infection in the UK, Europe, South Africa and the USA increases the risk of new cases with this variant arriving in New Zealand.
- The UK variant is increasingly becoming the dominant variant in the UK, and the US CDC predicts that it may become the dominant variant there by approximately April 2021. A small number of cases in New Zealand MIQ have been recorded so far, but this is likely to increase.
- New Zealand has imposed pre-departure testing for all long-haul returnees but this will not totally prevent cases of these variants arriving in New Zealand, although it may reduce the numbers arriving.
- Although there is emerging evidence of increased transmissibility there is no evidence on the need to change current quarantine Infection Prevention and Control procedures.
- If there is a breach from MIQ and community transmission occurs, it is likely to spread more rapidly and be more challenging to contain and also put pressure on contact tracing resources.
- As in other countries, in the setting of an outbreak rapid deployment of a vaccine should be considered to protect vulnerable groups (e.g., community clusters, vulnerable populations such as the elderly, and Maori and Pasifika communities) and potentially provide some reduction in transmission rates.

Ian G Town

Dr Ian Town

Chief Science Advisor

Next Steps	Advice sent to Medsafe January 20th

In the development of this work, the following parties have been consulted with:	s 9(2)(g)(ii) [redacted]
What are the implications and considerations of this advice on Te Tiriti o Waitangi and equity?	Not considered in detail

Resources used:		
Ministry of Health Policies and Procedures	☐ Yes ☒ No	
External Health Scientific organisations	☐ Yes ☒ No	
Existing database of RFAs	☐ Yes ☒ No	
Internal MH Advice	☒ Yes ☐ No	
External Expert Advice	☐ Yes ☒ No	
Literature Review	☒ Yes ☐ No	Abbreviated

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Medicine Evaluation; Non-Clinical Studies

FINAL

1 PRODUCT DETAILS

File number:	TT50-10853
Product name:	Comirnaty (COVID-19 mRNA vaccine) (Pfizer-BioNTech) 0.5 mg/mL concentrate for injection (TT50-10853).
Dose form:	Concentrate for injection
Drug substance and strength:	BNT162b2 [mRNA], 0.5 mg/mL (as 225 µg/0.45 mL) Each 0.3 mL dose of the diluted vaccine delivers 30 µg drug substance.

Evaluator: s 9(2)(g)(ii) [redacted]

By email to s 9(2)(g)(ii) [redacted]**, Acting Manager Product Regulation, Medsafe 28 Jan 2021 12:27 am**

Peer reviewer: s 9(2)(g)(ii) [redacted]

By email to s 9(2)(g)(ii) [redacted]**, Acting Manager Product Regulation, Medsafe 28 Jan 2021 10:32 am**

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Limited glossary / abbreviations

Abbreviation	Expansion
ACE2	Angiotensin Converting Enzyme 2 Receptor for
ADE	Antigen Dependent Enhancement
ALC-0159	2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide
ALC-0315	((4-hydroxybutyl) azanediyl) bis (hexane-6,1-diyl) bis(2-hexyldecanoate)
Bw;bwt	Bodyweight
DART	Developmental and Reproductive Toxicity
EM	Electron Microscopy
GMT	Geometric Mean Titre
HEK	Human Embryonic Kidney Cells
HCS	Human Convalescent Serum
IM	Intra muscular injection
IFN	Interferon
IL	Interleukin
LNP	Lipid Nano-Particles (specifically LNP8 unless otherwise specified)
MACS	Magnetic Antigen Cell Separation
MOE	Margin of Exposure
mRNA	messenger Ribonucleic acid
modRNA	nucleoside modified mRNA
OP	OroPharyngeal
P2	two proline mutations
pVN_{50}	A measure of the serum antibody Titre (The reciprocal of the serum dilution resulting in a 50% neutralization of a pseudo-virus). A higher value indicates a greater response/titre
pVNT	Pseudo Virus Neutralisation Titre
q.s.	Quatum satis
QSAR	Quantative Strutural Activity Relationship
RNA	Ribonucleic acid
RBD	Receptor Binding Domain
S protein	SARS-CoV-2 spike glycoprotein
TGA	Therapeutic Goods Administration (Australia)
Th1	T helper type 1 cells
Th2	T helper type 2 cells
TNF	Tumour Necrosis Factor
TTC	Threshold of Toxicological Concern
V8&9	Viral variants of SAR-CoV-2
VAERD	vaccine-associated enhanced respiratory disease

Non-Clinical Assessment

1 INTRODUCTION

This new medicine application is for a new biological entity, BNT162b2 [mRNA], hereafter referred to as BNT162b2 (BioNTech code number BNT162, Pfizer code number PF-07302048), developed by Pfizer and BioNTech. The drug product (COMIRNATY) is an RNA-based vaccine indicated for the active immunisation of individuals aged 16 (originally 18 in the TGA application but amended by the applicant) years and over against COVID-19 disease caused by the SARS-CoV-2 virus.

The vaccine will be administered intramuscularly (IM) in the upper arm (deltoid muscle) as a series of two 30 µg doses of the diluted vaccine solution (0.3 mL each) according to the following schedule: a single 0.3 mL dose followed by a second 0.3 mL dose 21 days later (prime/boost regimen).

The drug substance is a nucleoside-modified mRNA that encodes a prefusion stabilised full-length variant of the SARS-CoV-2 spike (S) glycoprotein and is manufactured by a cell-free *in vitro* transcription process. The final clinical variant and related developmental variant RNAs were encapsulated lipid nanoparticles (LNPs), which facilitate entry of the RNA into host cells. The RNA is translated in the host cells to the S protein, which induces a protective immune response in the vaccinated individual. The vaccine is formulated as a preservative-free concentrated suspension for injection, presented in a multi-dose vial. The product is supplied frozen (-80°C to -60°C) and must be thawed and diluted with sterile sodium chloride (0.9%) solution prior to administration.

s 6(b)(ii)

The LNP component of the Pfizer vaccine formulation contains two novel excipient lipids, ALC-0159 (2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide) and ALC-0315(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate). These lipids are a key aspect of the formulation contributing both to the particle size of LNPs and the stability of the mRNA in the formulation.

Memo

Date:	28 January 2021
To:	s 9(2)(g)(ii), MAAC Secretary, Product Regulation
Copy to:	s 9(2)(g)(ii), Acting Manager, Product Regulation
From:	s 9(2)(g)(ii) Team Leader – Medicines Assessment, Product Regulation
Subject:	**Referral to the Medicines Assessment Advisory Committee – Comirnaty (COVID-19 mRNA vaccine) (Pfizer-BioNTech) 0.5 mg/mL concentrate for injection (TT50-10853)**
For your:	Action

Purpose of the memo
Having completed the evaluation of an application for consent to distribute Comirnaty (COVID-19 mRNA vaccine) (Pfizer-BioNTech) 0.5 mg/mL concentrate for injection (TT50-10853), Medsafe is unable to recommend that the Minister's delegate grant consent to the distribution of the product.

You are therefore asked to administer the recommendation that the Minister's delegate refers this application to the Medicines Assessment Advisory Committee (MAAC) for consideration.

Background
A new medicine application was submitted by Pfizer New Zealand Limited for Comirnaty (COVID-19 mRNA vaccine) (Pfizer-BioNTech) 0.5 mg/mL concentrate for injection (TT50-10853) under section 20 of the Medicines Act 1981.

- The application is being considered for provisional consent under section 23 of the Medicines Act 1981 for the following indications:

  Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 16 years of age and older.

  The use of the vaccine must be in accordance with official recommendations.

- The application has been submitted via an expedited rolling review process and has been assessed under urgency due to the significant clinical need for a safe and effective COVID-19 vaccine. The initial application was received on 13 November 2020 after which a total of eight tranches of supporting information were submitted to Medsafe. Following assessment of these data packages, a request for additional information was issued on 15 January 2021 and response from Pfizer was received on 22 January 2021. Additional responses and data to support a change in the number of deliverable doses per vial were received on 27 January 2021. All additional data has since been assessed and a final recommendation has been made on 28 January 2021.
- Given the rapid development of this medicine and the urgent clinical need that exists in New Zealand, there are several aspects of data to support quality, safety and efficacy that are not available at the time of completion of the evaluation. It is therefore proposed to include requirements to submit this data to Medsafe within specified timeframes in the conditions of a possible provisional consent. It is also proposed that any provisional consent be granted for a period of x months, before which time all additional data should be received. See the attached final evaluation report for the proposed provisional consent conditions.

- It is requested that the MAAC focus on the specific aspects in their consideration of the application:
    - The conditions and consent time period proposed for provisional consent under section 23 of the Medicines Act 1981. Specifically, whether these are appropriate and sufficient given the data provided up to the time of referral, as well as whether any additional conditions should be applied.
    - Whether the benefit risk balance of Comirnaty vaccine for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 16 years of age and older is positive.
    - Whether to accept the proposed indications, or to request that the Sponsor update the New Zealand data sheet so that it is harmonised with the TGA approved product information, and includes the following indication:

      Comirnaty (BNT162b2 (mRNA)) COVID-19 vaccine has provisional consent for the indication below:

      Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 16 years of age and older.

      The use of this vaccine should be in accordance with official recommendations.

      The decision has been made on the basis of short-term efficacy and safety data. Continued approval depends on the evidence of longer-term efficacy and safety from ongoing clinical trials and post-market assessment.

Conclusions

The final conclusions and recommendations are described in full at the end of the attached evaluation reports. The following is the full list of evaluation reports and supporting documentation that are attached:

- Final evaluation report – Quality (includes final recommendation)
- Final evaluation reports – Novel excipients
- Final evaluation report – Non-clinical
- Final evaluation report – Clinical
- Final evaluation report – RMP
- Application dossier composed of iterative rolling review tranches and RFI responses and additional data
- TGA assessment documentation
- Advice from the Ministry of Health Science and Technical Advisory Group (STAG) on new SARS-CoV-2 virus strains and the implications for COVID-19 vaccines

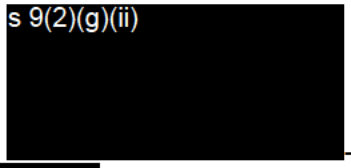
Recommendations

It is recommended that you:

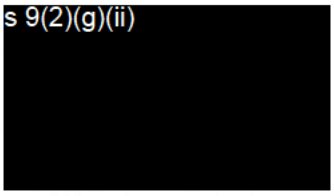
1.	Note	the attached evaluation reports and supporting documentation.	Yes / No
2.	Administer	the recommendation that the Minister's delegate refers this application to the Medicines Assessment Advisory Committee for consideration.	Yes / No

Signature  Date: 28 January 2021

s 9(2)(g)(ii)
Team Leader – Medicines Assessment, Product Regulation

Signature  Date: 28 January 2021

s 9(2)(g)(ii)
Acting Manager, Product Regulation

Signature  Date: 28.01.2021

s 9(2)(g)(ii)
MAAC Secretary, Product Regulation

MEDSAFE
NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY
A BUSINESS UNIT OF THE MINISTRY OF HEALTH

28 January 2021

133 Molesworth Street
PO Box 5013
Wellington 6140
New Zealand
T +64 4 496 2000

s 9(2)(a)
Senior Regulatory Affairs Associate
Pfizer Australia Pty Limited
c/ Pfizer New Zealand Limited
P O Box 3998
Auckland 1140

File Ref: TT50-10853

Dear s 9(2)(a)

Application for consent to distribute a new medicine under section 20 of the Medicines Act 1981 – Comirnaty (COVID-19 mRNA vaccine) (Pfizer-BioNTech) 0.5 mg/mL concentrate for injection (TT50-10853)

Evaluation of all information supplied in the application for consent to distribute the above product has been completed.

The processes undertaken to date included:

- an application was lodged with Medsafe under a rolling review process together with data to support the safety, efficacy, and quality of the product
- the application was evaluated by Medsafe
- during the assessment, there was one opportunity to address any issues and concerns.

Having reviewed the information supplied in your initial application and in your further response, I am not satisfied that I should give my consent to the distribution of the product.

Therefore, as provided by section 22(2) of the Medicines Act 1981 (the Act), I am referring your application to the Medicines Assessment Advisory Committee (the Committee) for consideration. The Committee is an independent, technical advisory committee established under section 8 of the Act to consider the risk benefit profile of the new medicine and report to the Minister of Health with a recommendation as to the decision that the Minister should make.

The Committee will consider this application at its 109th meeting to be held on 2 February 2021.

The Committee's operating rules allow up to three persons from the sponsor company to present their application to the Committee and to answer any queries posed by the Committee members. The meeting in general is held under the Chatham House Rule (http://www.chathamhouse.org.uk/about/chathamhouserule/).

During the meeting:

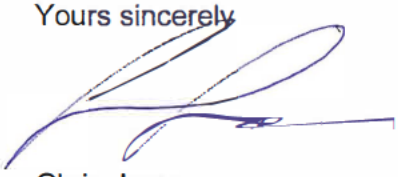
i. you will be given an opportunity to present your view of the overall risk benefit profile and any particular points that you wish to draw to the attention of the Committee. Presentations should be limited to a duration of ten minutes
ii. you may provide a justification to the Committee for the approval of the product

iii. the Committee may pose specific questions to you relating to your application, you will be given the opportunity to respond
iv. you will be required to exit from the meeting before the Committee develops a recommendation on the application.

Please note that new data not previously submitted to Medsafe may only be presented after the meeting in response to a specific request by the Committee.

If you would like to observe the meeting, please contact the MAAC Secretary at committees@health.govt.nz.

Yours sincerely



Chris James
Group Manager
Medsafe
as the Minister's delegate for section 22(2) of the Medicines Act 1981

Memo

MINISTRY OF HEALTH
MANATŪ HAUORA

Date:	3 February 2021
To:	Chris James, Minister's Delegate, Group Manager, Medsafe
Copy to:	
From:	s 9(2)(g)(ii) , Acting Manager, Product Regulation
Subject:	**Medicines Assessment Advisory Committee minutes and recommendations – 109th meeting on 2 February 2021**
For your:	Action and Decision

Background
This memo asks you to consider recommendations made to you by the Medicines Assessment Advisory Committee (MAAC), in your capacity as the Minister's delegate, for the purpose of granting consent to the distribution of medicines under sections 20 and 23 of the Medicines Act 1981 (the Act).

The MAAC is a Ministerial advisory committee established under section 8 of the Act to provide advice in relation to the approval of medicines.

Summary
The MAAC met on **2 February 2021** to consider applications you have previously referred to it under section 22(2) of the Act.

Attached is a copy of the ratified minutes of the 109th meeting of the MAAC, which include the Committee's recommendation as to the decision you should make in relation to the medicines considered. A summary of recommendations is also provided.

Action
The MAAC has recommended that you grant provisional consent to the distribution of the following medicine: Comirnaty (COVID 19 mRNA vaccine) (Pfizer BioNTech) 0.5 mg/mL concentrate for injection (TT50 10853). Medsafe supports this recommendation and you are therefore asked to sign the attached letter to the applicant company to advise them of the outcome of the MAAC recommendation.

Recommendations
It is recommended that you:

1.	Note	the minutes from the 109th meeting of the MAAC held on 2 February 2021.	Yes/No

2.	Sign	the attached letter to the applicant company, Pfizer New Zealand, advising them of the MAAC's recommendation that you grant provisional consent to the distribution of the medicine Comirnaty (COVID-19 mRNA vaccine) (Pfizer-BioNTech) 0.5 mg/mL concentrate for injection (TT50-10853)	Yes/No

Signature s 9(2)(g)(ii) Date: 3 Feb 2021

s 9(2)(g)(ii)

Acting Manager, Product Regulation

Signature Date: 3/2/2021

Chris James

Group Manager, Medsafe

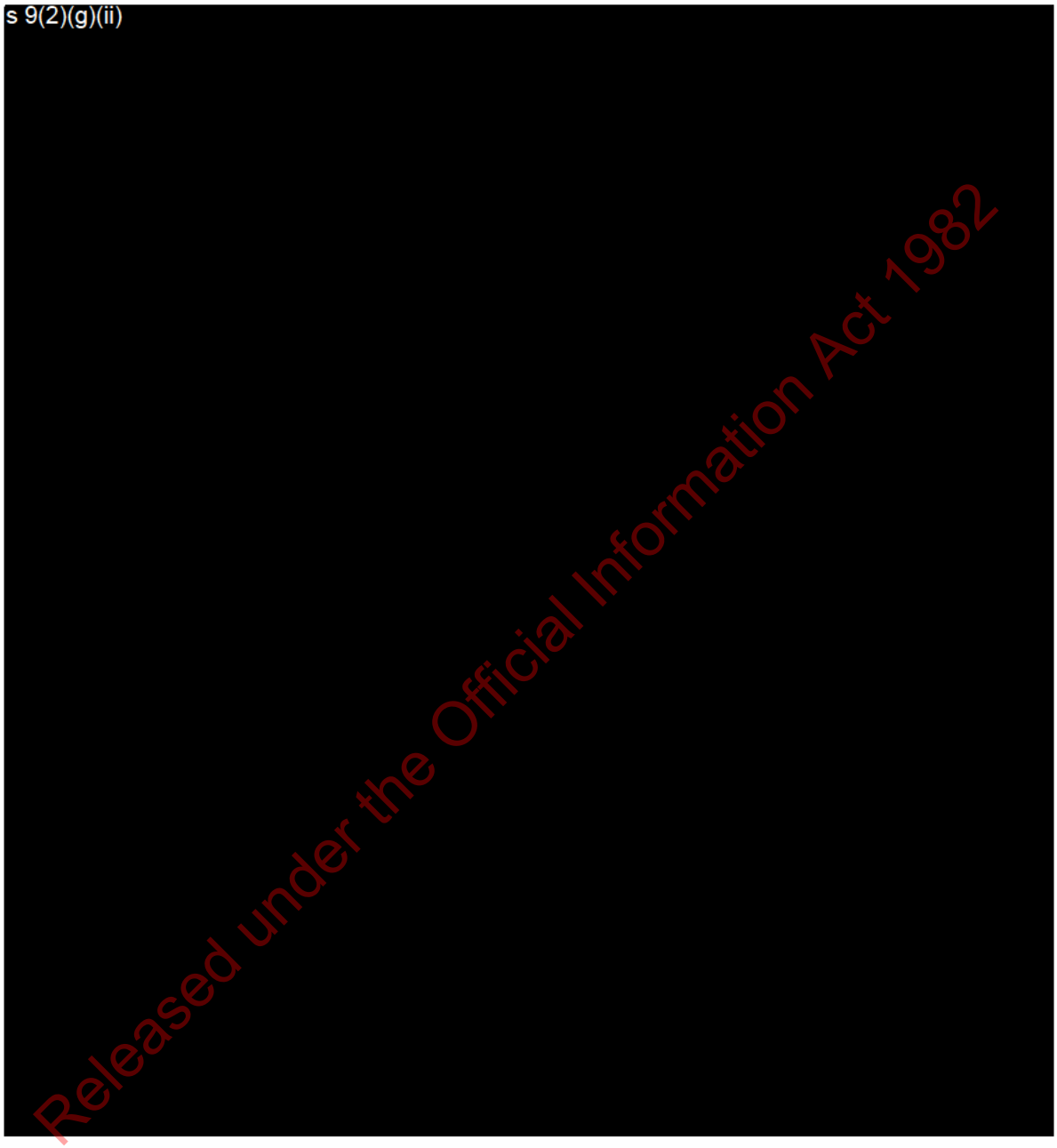
Medicines Assessment Advisory Committee

Minutes of the 109th meeting held on Tuesday 2 February 2021

Ministry of Health
Wellington

Minutes of the 109th meeting of the Medicines Assessment Advisory Committee by videoconference on 2 February 2021 at 9:30am

s 9(2)(g)(ii)



1 Welcome

The Chair opened the 109th meeting at 9:30am and welcomed members and guests to this extraordinary meeting to consider a recommendation on the approval of Comirnaty (COVID-19 mRNA vaccine) (Pfizer-BioNTech) 0.5 mg/mL concentrate for injection submitted by Pfizer New Zealand Limited. The Committee members introduced themselves.

2 Apologies

Apologies were received from s 9(2)(g)(ii) s 9(2)(g)(ii) as unavailable over the duration of the meeting.

4 Declaration of conflicts of interest

Members submitted their conflicts of interest forms to the Secretary.

The following new conflicts of interest were declared:

a. s 9(2)(g)(ii) before accessing the meeting documentation, had declared that she had shares in Pfizer, Moderna, Johnson & Johnson and Vitalis. This precluded her from accessing the meeting documentation and from attending the 109th meeting.

b. s 9(2)(g)(ii) declared he had shares in Ergomed and BLIS Technologies

All other members declared they had no additional interests that would pose a conflict with any of the items on the agenda.

The Committee agreed that, other than s 9(2)(g)(ii), there were no potential conflicts of interest that were considered likely to influence the discussion or decisions of the Committee at this meeting.

5 Applications for consent to distribute a new medicine under section 20/23 of the Medicines Act 1981 (referred by the Minister of Health under section 22(2))

5.1 Comirnaty (COVID-19 mRNA vaccine) (Pfizer-BioNTech) 0.5 mg/mL concentrate for injection (TT50-10853) Pfizer (NZ) Ltd

The Pfizer-BioNTech Covid-19 mRNA vaccine has been developed in response to the global pandemic of the SARS-COV-2 virus that causes Covid-19. This is the first application to market a Covid-19 vaccine in New Zealand and the first Covid-19 vaccine to be granted emergency use authorisations in the UK and the US. Australia provisionally approved this vaccine on 25 January 2021. Due to the continued global spread of the virus and its variants, availability of a vaccine is an important part of the New Zealand Government's Covid-19 strategy.

New Zealand does not have an emergency use authorisation pathway and currently does not have the public health emergency situation of many other countries, but this situation can change.

A new medicine application was submitted by Pfizer New Zealand Limited for Comirnaty (COVID-19 mRNA vaccine) (Pfizer-BioNTech) 0.5 mg/mL concentrate for injection (TT50-10853) under section 20 of the Medicines Act 1981.

The application is being considered for provisional consent under section 23 of the Medicines Act 1981 for the following indications:

> *Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 16 years of age and older.*
>
> *The use of the vaccine must be in accordance with official recommendations.*

The application has been submitted via an expedited rolling review process and has been assessed under urgency due to the significant clinical need for a COVID 19 vaccine with a positive benefit risk profile. The initial application was received on 13 November 2020, after which a total of eight tranches of supporting information were submitted to Medsafe. Following assessment of these data packages, a request for additional information was issued on 15 January 2021 and response from Pfizer was received on 22 January 2021. Additional responses and data to support a change in the number of deliverable doses per vial were received on 27 January 2021. All additional data has since been assessed and a final recommendation has been made on 28 January 2021.

Given the rapid development of this medicine and the urgent clinical need that exists in New Zealand, there are several aspects of the data required to support quality, safety and efficacy that are not available at the time of completion of the evaluation. It is also proposed that any provisional consent be granted for a period of nine months, before which time all additional data should be received.

It was requested that the Committee focus on the specific aspects in their consideration of the application:

- The conditions and consent time period proposed for provisional consent under section 23 of the Medicines Act 1981. Specifically, whether these are appropriate and sufficient given the data provided up to the time of referral, as well as whether any additional conditions should be applied.
- Whether the proposed indications for the medicine are appropriate and supported by the clinical data available, as well as whether any additional restrictions should be applied.

The following is the full list of evaluation reports and supporting documentation that were provided:

- Final evaluation report – Quality (includes final recommendation)
- Final evaluation report – Novel excipients
- Final evaluation report – Non-clinical
- Final evaluation report – Clinical
- Final evaluation report – RMP
- Application dossier composed of iterative rolling review tranches and RFI responses and additional data
- TGA assessment documentation

- Advice from the Ministry of Health Science and Technical Advisory Group (STAG) on new SARS-CoV-2 virus strains and the implications for COVID-19 vaccines

Pfizer New Zealand was informed of the referral on 29 January 2021.

Medsafe Presentation

Medsafe presented an overview of what is known about Comirnaty to the Committee.

Pre-clinical discussion

The Committee considered the following documentation:

- Final evaluation report Non-clinical

The Committee noted that the pre-clinical questions raised in the report were addressed satisfactorily by the company. The Committee noted that pre-clinical observations such as hepatoxicity are not apparent in the clinical data. The reactogenicity seen in the clinical data does not appear to be a concern in the pre-clinical data. The data on long terminal half-life of the lipid nanoparticles was considered unusual but unlikely to be a safety concern, as only two doses are intended to be administered. The pre-clinical data did not suggest safety concerns in pregnancy.

The Committee considers that generally the pre-clinical data has been superseded by the clinical data. The Committee had no safety concerns based on the preclinical data.

The Committee adopted the report and agreed with the conclusions.

Evaluation

- **Quality evaluation report (including Novel Excipients evaluation report)**

The Committee considered the following documentation:

  - Final evaluation report Quality (includes final recommendation)

The Committee noted that the Medsafe evaluation report was detailed and comprehensive. It was noted that many of the questions posed by Medsafe had been resolved and unresolved questions were included as conditions for the provisional consent.

The number of quality conditions was noted and that these conditions addressed instances where usual data was missing due to the developing nature of the vaccine. The quality conditions align with those required by other regulators, in particular the European Medicines Agency.

Medsafe noted that under Emergency Use Authorisation procedures, product released to the US and UK markets are from smaller batch sizes.

The scale difference of the potential New Zealand batches was a focus of the quality data assessment to ensure vaccine manufactured at commercial scale is comparable to clinical trial batches.

Pfizer has demonstrated that final product specifications are sufficient to ensure that product supplied to New Zealand will be comparable to clinical trial batches. Any gaps in product characterisation would be covered in the conditions of the provisional consent.

The Committee expressed confidence in the Medsafe quality and manufacturing evaluation and were interested in being kept informed of updates in this area.

- **Clinical evaluation report**

The Committee considered the following documentation:

  - Final evaluation report – Clinical

The Committee considered the issue of efficacy data for subpopulations. This subset included Maori, Asian, Pacific peoples, the elderly and groups who are immunocompromised. The Committee commented that the ethnicity subset data submitted was remarkably similar in efficacy and it is not unreasonable to assume there is no genetic reason for different responses in different ethnic groups in New Zealand.

The Committee agreed that it will be important to collect post-market safety data for Maori, Pacific peoples, elderly and immunocompromised subsets as these are the people who are more likely to be at higher risk of complications of COVID-19. However, the clinical picture on efficacy and safety will become clearer over time as more people receive the vaccine.

The Committee discussed the lack of data on the duration of response of the vaccine. Medsafe had asked the sponsor for an early cut-off time for more data, which was not available. The sponsor had confirmed that the next data analysis from the pivotal clinical trial will arrive in April 2021.

Overall, the Committee was satisfied with the clinical report and summary presented. The Committee was satisfied with the efficacy data to date acknowledging that more data will be available over time.

- **RMP evaluation report**

The Committee considered the following documentation:

  - Final evaluation report - RMP

The Committee considered that the latest version of the Risk Management Plan addresses many areas of concern raised by Medsafe. The need for additional safety information regarding the elderly, children, people with comorbidities and immunocompromised people was emphasised.

The Committee noted that patients with autoimmune diseases and patients who are immunosuppressed were not well represented in clinical trials. The planned clinical study in patients with rheumatoid arthritis receiving

immunomodulators was noted. The Committee expressed concern that these individuals might be among those prioritised for vaccination before the results of this study are available. It was noted that this issue is to be managed as part of the Ministry of Health immunisation implementation programme.

The need for more information on potential safety signals such as reactogenicity, anaphylaxis, vaccine-associated enhanced disease and facial paralysis was noted.

The Committee was satisfied with the updated Risk Management Plan, noting that additional clinical studies, pharmacovigilance activities and monthly safety reports are planned to address areas of missing information.

The Committee accepted the Risk Management Plan as written, noting that it is a living document and there is the opportunity to add safety concerns as they emerge.

Discussion with Pfizer

Pfizer representatives joined the meeting to respond to questions from the Committee. The Committee had questions regarding finished product testing, risk of transport to New Zealand, in use data in specific populations, use in severe COVID-19, the emergence of new variants, unforeseen safety signals after the doses given to date, update on duration of protection and the new 6 dose proposal. All questions were suitably addressed by Pfizer.

Discussion to finalise recommendation

Provisional Consent

The Committee unanimously agreed to Medsafe's proposal to grant provisional consent with a one-month period. This period was proposed to ensure that all post-approval data commitment deadlines were met. The Committee agreed with this rationale.

Indications

The Committee agreed that the proposed indication wording for Comirnaty is revised to the following:

> *Comirnaty has provisional consent (see section 5.1) for the indication below:*
>
> *Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 16 years of age and older.*
>
> *The use of this vaccine should be in accordance with official recommendations.*

The committee discussed the likely real world use in New Zealand and acknowledged that the vaccine roll-out will be managed by the Ministry of Health.

The Committee suggested that Section 5.1 of the data sheet to be revised to include the following statement:

> *This medicine has been given a provisional consent under Section 23 of the Act. This means that further evidence on this medicine is awaited or that there are specific conditions of use. Refer to the consent notice published in the New Zealand Gazette for the specific conditions.*

Conditions of provisional consent

The Committee reviewed each proposed condition of the provisional consent. The Committee agreed that Medsafe could make technical amendments to the conditions of consent.

The Committee agreed to the addition of the following condition:

> *Provide independent batch certification, such as UK National Institute for Biological Standards and Control (NIBSC) certification, EU Official Control Authority Batch Release (OCABR) certification, Australian TGA batch release assessment, or any other certification agreed with Medsafe, on request for all batches distributed in New Zealand.*

The Committee raised concerns regarding the wording of the following conditions.

> *Provide regular updates on the duration of efficacy and the requirement for booster doses. This should include the six months analysis data from Study C4591001. Interim report due: April 2021.*
>
> *Provide updates on efficacy including regarding asymptomatic infection in the vaccinated group, vaccine failure, immunogenicity, efficacy in population subgroups and results from post-marketing studies, when these become available.*
>
> *Submit the final Clinical Study Reports for Study C4591001 and Study BNT162-01 once they available.*
>
> *Inform Medsafe of all safety reviews they conduct or become aware of and provide the completed review.*

The Committee recommended the following amendments to the conditions to improve clarity of the requirements:

> *Provide regular reports on the duration of efficacy and the requirement for booster doses within five working days of these being produced.*

Provide the six months analysis data from Study C4591001. Report due: April 2021.

Provide any reports on efficacy including regarding asymptomatic infection in the vaccinated group, vaccine failure, immunogenicity, efficacy in population subgroups and results from post-marketing studies, within five working days of these being produced.

Provide the final Clinical Study Reports for Study C4591001 and Study BNT162-01 within five working days of these being produced.

Provide monthly safety reports, as well as all safety reviews they conduct or become aware of.

Recommendation

The Committee recommended that the Minister of Health should grant provisional consent to distribute this medicine under Section 23 of the Medicines Act 1981 and impose the conditions proposed by Medsafe as amended by the Committee. The Committee recommended that the provisional consent should have an effect of nine months.

General Business

The Chair thanks s 9(2)(g)(ii) for his services to the Committee and wishes him well in his future endeavours.

Date of Next Meeting
No date has been set.

There being no further business, the Chair thanked members and guests for their attendance and closed the meeting at 2.14pm.

CHAIR'S SIGNATURE: s 9(2)(g)(ii) [redacted]

DATE: 03/02/2021

This document was prepared and written by
s 9(2)(g)(ii) [redacted]
the Medicines Assessment Advisory Committee Secretary

SUMMARY OF RECOMMENDATIONS FROM THE 109TH MEETING OF THE MEDICINES ASSESSMENT ADVISORY COMMITTEE HELD IN WELLINGTON ON TUESDAY 2 FEBRUARY 2021 AT 9:30 AM

4. Applications for consent to distribute a new medicine under section 23 of the Medicines Act 1981 (referred by the Minister of Health under section 22(2))

4.1 The Committee recommended that the Minister of Health should grant provisional consent to distribute this medicine under Section 23 of the Medicines Act 1981 and impose the conditions proposed by Medsafe as amended by the Committee. The Committee recommended that the provisional consent should have an effect of nine months.

.

Extract from the minutes of the 109th meeting
of the Medicines Assessment Advisory Committee
held in Wellington
on 2 February 2021 commencing at 9:30am

Comirnaty (COVID-19 mRNA vaccine) (Pfizer-BioNTech) 0.5 mg/mL concentrate for injection (TT50-10853)
Pfizer (NZ) Ltd

The Pfizer-BioNTech Covid-19 mRNA vaccine has been developed in response to the global pandemic of the SARS-COV-2 virus that causes Covid-19. This is the first application to market a Covid-19 vaccine in New Zealand and the first Covid-19 vaccine to be granted emergency use authorisations in the UK and the US. Australia provisionally approved this vaccine on 25 February 2021. Due to the continued global spread of the virus and its variants, availability of a vaccine is an important part of the New Zealand Government's Covid-19 strategy.

New Zealand does not have an emergency use authorisation pathway and currently does not have the public health emergency situation of many other countries, but this situation can change.

A new medicine application was submitted by Pfizer New Zealand Limited for Comirnaty (COVID-19 mRNA vaccine) (Pfizer-BioNTech) 0.5 mg/mL concentrate for injection (TT50 10853) under section 20 of the Medicines Act 1981.

The application is being considered for provisional consent under section 23 of the Medicines Act 1981 for the following indications:

> *Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 16 years of age and older.*
>
> *The use of the vaccine must be in accordance with official recommendations.*

The application has been submitted via an expedited rolling review process and has been assessed under urgency due to the significant clinical need for a COVID-19 vaccine with a positive benefit-risk profile. The initial application was received on 13 November 2020, after which a total of eight tranches of supporting information were submitted to Medsafe. Following assessment of these data packages, a request for additional information was issued on 15 January 2021 and response from Pfizer was received on 22 January 2021. Additional responses and data to support a change in the number of deliverable doses per vial were received on 27 January 2021. All additional data has since been assessed and a final recommendation has been made on 28 January 2021.

Given the rapid development of this medicine and the urgent clinical need that exists in New Zealand, there are several aspects of the data required to support quality, safety and efficacy that are not available at the time of completion of the evaluation. It is also proposed that any provisional consent be granted for a period of nine months, before which time all additional data should be received.

It was requested that the Committee focus on the specific aspects in their consideration of the application:

- The conditions and consent time period proposed for provisional consent under section 23 of the Medicines Act 1981. Specifically, whether these are appropriate and sufficient given

133 Molesworth Street
PO Box 5013
Wellington 6140
New Zealand
T +64 4 496 2000
W www.medsafe.govt.nz

3 February 2021

s 9(2)(a)
Senior Regulatory Affairs Associate, Global Regulatory Affairs – International
Pfizer New Zealand Limited
P O Box 3998
AUCKLAND 1140

File Ref: TT50 10853

Dear s 9(2)(a)

MAAC recommendation to grant provisional consent to distribute a new medicine under section 23 of the Medicines Act 1981 – Comirnaty (COVID-19 mRNA vaccine) (Pfizer-BioNTech) 0.5 mg/mL concentrate for injection (TT50-10853)

This letter is to notify you that your application for consent to distribute the above medicine was referred to the Medicines Assessment Advisory Committee (MAAC) and considered at its meeting held on 2 February 2021.

The Committee's recommendation is that I, as the Minister's delegate, should grant provisional consent to the distribution of the medicine. I agree with the MAAC's recommendation and a provisional consent notice will be submitted for publication in the *New Zealand Gazette.* Please confirm with the MAAC Secretary (at committees@health.govt.nz), that the details in the enclosed Therapeutic Product Database Report are correct.

Please note that the provisional consent to distribute a medicine does not take effect until the date of publication of the *Gazette* notice. Electronic copies of the final data sheet(s) and declaration form(s) must be submitted to Medsafe within 10 days of publication of the *Gazette* notice. You will be sent a letter advising you when publication has occurred, with a copy of the *Gazette* notice enclosed.

Yours sincerely

Chris James
Group Manager
Medsafe
as the Minister's delegate for section 20/23 of the Medicines Act 1981

133 Molesworth Street
PO Box 5013
Wellington 6140
New Zealand
T +64 4 496 2000
W www.medsafe.govt.nz

3 February 2021

s 9(2)(a)
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Pfizer New Zealand Limited
P O Box 3998
AUCKLAND 1140

File Ref: TT50-10853

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Chris James
Group Manager
Medsafe
as the Minister's delegate for section 20/23 of the Medicines Act 1981

Extract from the minutes of the 109th meeting
of the Medicines Assessment Advisory Committee
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> *Active immunisation to prevent coronavirus disease 2019 (COVID 19) caused by SARS-CoV-2, in individuals 16 years of age and older.*
>
> *The use of the vaccine must be in accordance with official recommendations.*

The application has been submitted via an expedited rolling review process and has been assessed under urgency due to the significant clinical need for a COVID 19 vaccine with a positive benefit risk profile. The initial application was received on 13 November 2020, after which a total of eight tranches of supporting information were submitted to Medsafe. Following assessment of these data packages, a request for additional information was issued on 15 January 2021 and response from Pfizer was received on 22 January 2021. Additional responses and data to support a change in the number of deliverable doses per vial were received on 27 January 2021. All additional data has since been assessed and a final recommendation has been made on 28 January 2021.

Given the rapid development of this medicine and the urgent clinical need that exists in New Zealand, there are several aspects of the data required to support quality, safety and efficacy that are not available at the time of completion of the evaluation. It is also proposed that any provisional consent be granted for a period of nine months, before which time all additional data should be received.

It was requested that the Committee focus on the specific aspects in their consideration of the application:

- The conditions and consent time period proposed for provisional consent under section 23 of the Medicines Act 1981. Specifically, whether these are appropriate and sufficient given

the data provided up to the time of referral, as well as whether any additional conditions should be applied Final evaluation report – Quality (includes final recommendation)

- Whether the proposed indications for the medicine are appropriate and supported by the clinical data available, as well as whether any additional restrictions should be applied.

The following is the full list of evaluation reports and supporting documentation that were provided:

- Final evaluation report – Quality (includes final recommendation)
- Final evaluation report – Novel excipients
- Final evaluation report – Non-clinical
- Final evaluation report – Clinical
- Final evaluation report – RMP
- Application dossier composed of iterative rolling review tranches and RFI responses and additional data
- TGA assessment documentation
- Advice from the Ministry of Health Science and Technical Advisory Group (STAG) on new SARS-CoV-2 virus strains and the implications for COVID-19 vaccines

Pfizer New Zealand was informed of the referral on 29 January 2021.

Medsafe Presentation

Medsafe presented an overview of what is known about Comirnaty to the Committee.

Pre-clinical discussion

The Committee considered the following documentation:

- Final evaluation report – Non-clinical

The Committee noted that the pre-clinical questions raised in the report were addressed satisfactorily by the company. The Committee noted that pre-clinical observations such as hepatoxicity are not apparent in the clinical data. The reactogenicity seen in the clinical data does not appear to be a concern in the pre-clinical data. The data on long terminal half-life of the lipid nanoparticles was considered unusual but unlikely to be a safety concern, as only two doses are intended to be administered. The pre-clinical data did not suggest safety concerns in pregnancy.

The Committee considers that generally the pre-clinical data has been superseded by the clinical data. The Committee had no safety concerns based on the preclinical data.

The Committee adopted the report and agreed with the conclusions.

Evaluation

- **Quality evaluation report (including Novel Excipients evaluation report)**

The Committee considered the following documentation:

- Final evaluation report – Quality (includes final recommendation)

The Committee noted that the Medsafe evaluation report was detailed and comprehensive. It was noted that many of the questions posed by Medsafe had been resolved and unresolved questions were included as conditions for the provisional consent.

The number of quality conditions was noted and that these conditions addressed instances where usual data was missing due to the developing nature of the vaccine. The quality conditions align with those required by other regulators, in particular the European Medicines Agency.

Medsafe noted that under Emergency Use Authorisation procedures, product released to the US and UK markets are from smaller batch sizes. The scale difference of the potential New Zealand batches was a focus of the quality data assessment to ensure vaccine manufactured at commercial scale is comparable to clinical trial batches.

Pfizer has demonstrated that final product specifications are sufficient to ensure that product supplied to New Zealand will be comparable to clinical trial batches. Any gaps in product characterisation would be covered in the conditions of the provisional consent.

The Committee expressed confidence in the Medsafe quality and manufacturing evaluation and were interested in being kept informed of updates in this area.

- **Clinical evaluation report**

The Committee considered the following documentation:

  - Final evaluation report – Clinical

The Committee considered the issue of efficacy data for subpopulations. This subset included Maori, Asian, Pacific peoples, the elderly and groups who are immunocompromised. The Committee commented that the ethnicity subset data submitted was remarkably similar in efficacy and it is not unreasonable to assume there is no genetic reason for different responses in different ethnic groups in New Zealand.

The Committee agreed that it will be important to collect post market safety data for Maori, Pacific peoples, elderly and immunocompromised subsets as these are the people who are more likely to be at higher risk of complications of COVID-19. However, the clinical picture on efficacy and safety will become clearer over time as more people receive the vaccine.

The Committee discussed the lack of data on the duration of response of the vaccine. Medsafe had asked the sponsor for an early cut-off time for more data, which was not available. The sponsor had confirmed that the next data analysis from the pivotal clinical trial will arrive in April 2021.

Overall, the Committee was satisfied with the clinical report and summary presented. The Committee was satisfied with the efficacy data to date acknowledging that more data will be available over time.

- **RMP evaluation report**

The Committee considered the following documentation:

  - Final evaluation report - RMP

The Committee considered that the latest version of the Risk Management Plan addresses many areas of concern raised by Medsafe. The need for additional safety information regarding the elderly, children, people with comorbidities and immunocompromised people was emphasised.

The Committee noted that patients with autoimmune diseases and patients who are immunosuppressed were not well represented in clinical trials. The planned clinical study in patients with rheumatoid arthritis receiving immunomodulators was noted. The Committee expressed concern that these individuals might be among those prioritised for vaccination before the results of this study are available. It was noted that this issue is to be managed as part of the Ministry of Health immunisation implementation programme.

The need for more information on potential safety signals such as reactogenicity, anaphylaxis, vaccine associated enhanced disease and facial paralysis was noted.

The Committee was satisfied with the updated Risk Management Plan, noting that additional clinical studies, pharmacovigilance activities and monthly safety reports are planned to address areas of missing information.

The Committee accepted the Risk Management Plan as written, noting that it is a living document and there is the opportunity to add safety concerns as they emerge.

Discussion with Pfizer

Pfizer representatives joined the meeting to respond to questions from the Committee. The Committee had questions regarding finished product testing, risk of transport to New Zealand, in use data in specific populations, use in severe COVID-19, the emergence of new variants, unforeseen safety signals after the doses given to date, update on duration of protection and the new 6 dose proposal. All questions were suitably addressed by Pfizer.

Discussion to finalise recommendation

Provisional Consent

The Committee unanimously agreed to Medsafe's proposal to grant provisional consent with a nine month period. This period was proposed to ensure that all post approval data commitment deadlines were met. The Committee agreed with this rationale.

Indications

The Committee agreed that the proposed indication wording for Comirnaty is revised to the following:

> *Comirnaty has provisional consent (see section 5.1) for the indication below:*
>
> *Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 16 years of age and older.*
>
> *The use of this vaccine should be in accordance with official recommendations.*

The committee discussed the likely real world use in New Zealand and acknowledged that the vaccine roll out will be managed by the Ministry of Health.

The Committee suggested that Section 5.1 of the data sheet to be revised to include the following statement:

> *This medicine has been given a provisional consent under Section 23 of the Act. This means that further evidence on this medicine is awaited or that there are specific conditions of use. Refer to the consent notice published in the New Zealand Gazette for the specific conditions.*

Conditions of provisional consent

The Committee reviewed each proposed condition of the provisional consent. The Committee agreed that Medsafe could make technical amendments to the conditions of consent.

The Committee agreed to the addition of the following condition:

> *Provide independent batch certification, such as UK National Institute for Biological Standards and Control (NIBSC) certification, EU Official Control Authority Batch Release (OCABR) certification, Australian TGA batch release assessment, or any other certification agreed with Medsafe, on request for all batches distributed in New Zealand.*

The Committee raised concerns regarding the wording of the following conditions.

> *Provide regular updates on the duration of efficacy and the requirement for booster doses. This should include the six months analysis data from Study C4591001. Interim report due: April 2021.*
>
> *Provide updates on efficacy including regarding asymptomatic infection in the vaccinated group, vaccine failure, immunogenicity, efficacy in population subgroups and results from post-marketing studies, when these become available.*
>
> *Submit the final Clinical Study Reports for Study C4591001 and Study BNT162-01 once they available.*
>
> *Inform Medsafe of all safety reviews they conduct or become aware of and provide the completed review.*

The Committee recommended the following amendments to the conditions to improve clarity of the requirements:

> *Provide regular reports on the duration of efficacy and the requirement for booster doses within five working days of these being produced.*
>
> *Provide the six months analysis data from Study C4591001. Report due: April 2021.*
>
> *Provide any reports on efficacy including regarding asymptomatic infection in the vaccinated group, vaccine failure, immunogenicity, efficacy in population subgroups and results from post-marketing studies, within five working days of these being produced.*
>
> *Provide the final Clinical Study Reports for Study C4591001 and Study BNT162-01 within five working days of these being produced.*
>
> *Provide monthly safety reports, as well as all safety reviews they conduct or become aware of.*

Recommendation

The Committee recommended that the Minister of Health should grant provisional consent to distribute this medicine under Section 23 of the Medicines Act 1981 and impose the conditions proposed by Medsafe as amended by the Committee. The Committee recommended that the provisional consent should have an effect of nine months.

NEW MEDICINE APPLICATION FORM
PRESCRIPTION MEDICINE

One copy of this form must be completed for each separate prescription medicine (name + dose form + drug substance(s) + strength + classification + flavour, as applicable). If there is an over-the-counter (OTC) classification of the same medicine, then the New Medicine Application form – OTC Medicine must be used.

The Guide to completing a New Medicine Application – Prescription Medicine form (Application Guide) referred to in this form is available on the Medsafe website as a separate document. Please do not submit the Application Guide document to Medsafe.

The macro enabled form is no longer available for use.

1. Proposed product details, required for all applications

Type of application: **New Medicine Application**

Type of high risk medicine (if applicable):

- Biological or biotechnological ☐
- Vaccine ☒
- Blood product ☐

Proposed trade name: **TBD**

Identifier (if the proposed trade name is the drug substance name):

Drug substance: **BNT162b2 [mRNA]** Please note, this is an interim drug substance name until an international non-proprietary name (INN) is assigned.

Dose form (refer to Application Guide): **Injection, concentrated**

Strength (include units): **30 micrograms/0.3 mL**

New Zealand Classification (refer to Application Guide): **Prescription**

Route of administration (refer to Application Guide): **Intramuscular**

ATC classification (refer to Application Guide): **TBD**

Proposed indications:

Active immunisation against COVID-19 disease caused by SARS-CoV-2 virus in individuals aged 16 years and over.

New Zealand Medicines Terminology:

A New Zealand Medicines Terminology Listing Certificate should be provided as part of the Medsafe application process.

The New Zealand Medicines Terminology Listing Certification has been attached ☒

This application form includes information relating to the full dossier, following submission of all 'rolls'. The New Zealand Medicines Terminology Listing Certificate will not be provided in the initial roll.

(Refer to http://www.nzulm.org.nz or email listings@nzmt.org.nz for further details on NZMT listings)

2. Additional information, where applicable:

- **All products**

The product is currently approved in the following countries: **N/A**

The product is currently pending approval in the following countries: **European Union, Canada, Switzerland and Australia.**

- **Clinical data including bioequivalence studies (if applicable)**

If bioequivalence studies were performed, indicate the following, where applicable:

New Zealand reference product and strength with which the biostudy was conducted: **N/A**

Australian reference product and strength with which the biostudy was conducted: **N/A**

Other reference product and strength with which the biostudy was conducted: **N/A**

- **Application based on a parent product**

If this application is a line extension for another product, provide the parent product details:

Parent product name: **N/A**

Parent product dose form: **N/A**

Parent product strength: **N/A**

Parent product classification: **N/A**

Additional application, submitted concurrently with the parent product: ☐ **N/A**

Indicate the difference between the parent product and the new product (refer to Application Guide): **N/A**

Parent product file number(s), if known: TT50- **N/A**

Details of 'parent product' sponsor(s): **N/A**

Full access to the rights to the product(s) has been provided by the sponsor(s) of the 'parent product': **N/A**

Comments: **N/A**

- **Application based on an overseas approval (abbreviated process)**

If this application is for consent to distribute a new product that was approved by one of the recognised regulatory authorities since 2001, and the reports from that process have been provided, indicate the following:

Regulatory authority name: **N/A**

Regulatory authority country:

If EU, specify the procedure used:

3. Applicant and Sponsor details

New Zealand Sponsor

Name and street address:

Pfizer New Zealand Limited
Level 1, Suite 1.4
Building B
8 Nugent Street
Grafton
Auckland 1023

Postal address (eg. PO Box):

Pfizer New Zealand Limited
PO Box 3998
Auckland 1140

Contact phone number: s 9(2)(a) [redacted]

Applicant

All correspondence relating to the application (including the invoice) will be sent to this person.

Name and designation of the person submitting this application:

s 9(2)(a) [redacted]
Senior Regulatory Affairs Associate

Postal address:

Pfizer Australia
Level 15-18, 151 Clarence Street
Sydney NSW 2000
Australia

Email address: s 9(2)(a) [redacted] Pfizer.com with a copy to RegulatoryAffairs.ANZ@Pfizer.com

Contact phone number: s 9(2)(a) [redacted]

4. Fees and Invoice details

Calculated Fee: NZD 102,210

Comments: **New Medicine Application**

All fees are GST inclusive.

Enter customer reference required on the invoice here (max 20 characters):
Pfz_Covid_NMA_2020

NB: All acknowledgement letters and invoices will be emailed but not sent in hard copy.

5. Product formulation:

Name of ingredient (For drug substance, identify amount equivalent to free base, if applicable)	**Type of ingredient**	**Quantity** (specify units)	**Quality standard**
Component name (if applicable)			
BNT162b2 [mRNA]	Active ingredient	s 9(2)(b)(ii)	
ALC-0315 [1]	Excipient - Functional lipid		
ALC-0159 [2]	Excipient - Functional lipid		
DSPC [3]	Excipient - Structural lipid		
Cholesterol	Excipient - Structural lipid		
Sucrose	Excipient - Cryoprotectant		
NaCl	Excipient - Buffer		
KCl	Excipient - Buffer		
$Na_2HPO_4*2H_2O$	Excipient - Buffer		
KH_2PO_4	Excipient - Buffer		
Water for injections	Excipient - Solvent/Vehicle		

[1] ALC-0315 = ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
[2] ALC-0159 = 2-[(polyethylene glycol)-2000]-*N,N*-ditetradecylacetamide
[3] DSPC = 1,2-Distearoyl-*sn*-glycero-3-phosphocholine

Proprietary ingredients

- If the quantitative formulation of any proprietary ingredients has been previously provided to Medsafe, list the proprietary ingredient name and the associated reference number(s): **N/A**
- If the quantitative formulation of any proprietary ingredients has not been previously provided to Medsafe, this information is presented in Module 3 on page: **N/A**
- If the quantitative formulation of any proprietary ingredients has not been previously provided to Medsafe, but this information will be sent directly from the supplier, list the ingredient name, identifier, and supplier: **N/A**

6. Product packaging, patient information, and storage conditions:

Container closure system and administration device:	Primary container: **Vial** Materials and description: **Clear Type I glass** Closure: **Rubber stopper, aluminium overseal and flip off cap.** Materials and description: **Stopper is composed of Datwyler FM457 gray bromobutyl rubber that is not manufactured from dry natural rubber (latex).**			
	Secondary container: **Carton** Materials and description: **cardboard**			
	Administration device: **N/A** Materials and description:			
Pack size(s) to be registered:	**195 vials**			
A package insert is to be supplied with the product:	**Yes**			
Proposed shelf life and storage conditions:	Protect from light	Protect from moisture	Do not refrigerate	Do not freeze
6 months stored in the freezer at -80°C to -60°C.	☒	☐	☐	☐
Undiluted or thawed vials may be stored at room temperature for no more than 2 hours, or in the refrigerator at 2ºC to 8ºC for up to 5 days. Do not refreeze thawed vials.	☐	☐	☐	☒
After dilution, store at 2°C to 25°C and use within 6 hours.	☐	☐	☐	☒
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

7. Production

Manufacturing of the drug substance

Name of drug substance	BNT162b2 [mRNA]
Name of manufacturer	BioNTech Manufacturing GmbH
Manufacturing site address	An der Goldgrube 12, 55131 Mainz, Germany
Regulatory authority which issued the GMP evidence	TGA
GMP evidence date of expiry	Clearance application under review MI-2020-CL-10905-1
DMF number, if known Or Certificate of Suitability number	TT60- R -CEP - -Rev
Letter of access provided	☐

Name of drug substance	BNT162b2 [mRNA]
Name of manufacturer	Rentschler Biotechnologie GmbH & Co. KG
Manufacturing site address	Erwin-Rentschler-Strasse 21, 88471 Laupheim, Germany
Regulatory authority which issued the GMP evidence	TGA
GMP evidence date of expiry	Clearance application under review MI-2020-CL-10912-1
DMF number, if known Or Certificate of Suitability number	TT60- R -CEP - -Rev
Letter of access provided	☐

Name of drug substance	BNT162b2 [mRNA]
Name of manufacturer	Wyeth BioPharma Division of Wyeth
Manufacturing site address	1 Burtt Road, Andover, MA 01810, USA
Regulatory authority which issued the GMP evidence	TGA
GMP evidence date of expiry	TGA clearance will be sought
DMF number, if known	TT60-

Or Certificate of Suitability number	R -CEP - -Rev
Letter of access provided	☐

Name of drug substance	BNT162b2 [mRNA]
Name of manufacturer	Pfizer Inc.
Manufacturing site address	875 Chesterfield Parkway West, Chesterfield, 63017-1732, USA
Regulatory authority which issued the GMP evidence	TGA
GMP evidence date of expiry	Clearance application under review MI-2020-CL-10943-1
DMF number, if known Or Certificate of Suitability number	TT60- R -CEP - -Rev
Letter of access provided	☐

Name of drug substance	BNT162b2 [mRNA]
Name of manufacturer	BioNTech Innovative Manufacturing Services GmbH
Manufacturing site address	Vollmersbachstraße 66 55743 Idar-Oberstein, Germany
Regulatory authority which issued the GMP evidence	TGA
GMP evidence date of expiry	Clearance application under review MI-2020-CL-10909-1
DMF number, if known Or Certificate of Suitability number	TT60- R -CEP - -Rev
Letter of access provided	☐

Manufacturing of the drug product

Name of manufacturer	Pfizer Manufacturing Belgium NV
Manufacturing site address	Rijksweg 12, 2870 Puurs, Belgium
Regulatory authority which issued the GMP evidence	TGA
GMP evidence date of expiry	MI-2019-CL-00824-1, expires 20-Apr-2021

Manufacturing steps carried out at this site	DP manufacturing Storage Final release for market supply

Name of manufacturer	Pharmacia and Upjohn Company LLC
Manufacturing site address	7000 Portage Road Kalamazoo, Michigan 49001 USA
Regulatory authority which issued the GMP evidence	TGA
GMP evidence date of expiry	MI-2020-CL-00411-1, expires 21 Sep 2021
Manufacturing steps carried out at this site	DP manufacturing Storage Final release for market supply

Name of manufacturer	BioNTech Manufacturing GmbH
Manufacturing site address	An der Goldgrube 12, 55131 Mainz, Germany
Regulatory authority which issued the GMP evidence	TGA
GMP evidence date of expiry	Clearance application under review MI-2020-CL-10922-1
Testing steps carried out at this site	Final release for market supply

Name of manufacturer	Pfizer Pharma GmbH Betriebsstätte Karlsruhe
Manufacturing site address	An der Tagweide 5, 76139 Karlsruhe, Germany
Regulatory authority which issued the GMP evidence	TGA

GMP evidence date of expiry	TGA clearance will be sought
Testing steps carried out at this site	DP storage

Packing of the drug product

Name of packer	Pfizer Manufacturing Belgium NV
Site address	Rijksweg 12, 2870 Puurs, Belgium
Regulatory authority which issued the GMP evidence	TGA
GMP evidence date of expiry	MI-2019-CL-00824-1, expires 20-Apr-2021
Packing steps carried out at this site	Primary & secondary packaging

Name of packer	Pharmacia and Upjohn Company LLC
Site address	7000 Portage Road Kalamazoo, Michigan 49001 USA
Regulatory authority which issued the GMP evidence	TGA
GMP evidence date of expiry	MI-2020-CL-00411-1, expires 21 Sep 2021
Packing steps carried out at this site	Primary & secondary packaging

Testing of the drug product

Name of testing site	Pfizer Manufacturing Belgium NV
Address	Rijksweg 12, 2870 Puurs, Belgium
Regulatory authority which issued the GMP evidence	TGA
GMP evidence date of expiry	Current clearance variation application under review MI-2020-CL-10925-1

Testing steps carried out at this site	DP release and stability testing: Endotoxin and Sterility

Name of testing site	Pfizer Ireland Pharmaceuticals
Address	Grange Castle Business Park, Clondalkin, Dublin 22, Ireland
Regulatory authority which issued the GMP evidence	TGA
GMP evidence date of expiry	MI-2017-CL-00823-1, expires 09-May-2022
Testing steps carried out at this site	DP release testing: Identity

Name of testing site	Wyeth BioPharma Division of Wyeth
Address	1 Burtt Road, Andover, MA 01810, USA
Regulatory authority which issued the GMP evidence	TGA
GMP evidence date of expiry	MI-2020-CL02177-1, expires 18-Jul-2022
Testing steps carried out at this site	DP release and stability testing: remaining parameters

Name of testing site	Pfizer Inc.
Address	875 Chesterfield Parkway West, Chesterfield, 63017-1732, USA
Regulatory authority which issued the GMP evidence	TGA
GMP evidence date of expiry	Clearance application under review MI-2020-CL-10943-1
Testing steps carried out at this site	DP release and stability testing: remaining parameters

Name of testing site	Pharmacia and Upjohn Company LLC
Address	7000 Portage Road Kalamazoo, Michigan 49001

	USA
Regulatory authority which issued the GMP evidence	TGA
GMP evidence date of expiry	MI-2020-CL-00411-1, expires 21 Sep 2021
Testing steps carried out at this site	DP release and stability testing: Endotoxin and Sterility

Biostudy/clinical site (if applicable)

Name of testing site	**N/A**
Address	

Bioanalytical testing site (if applicable)

Name of testing site	**N/A**
Address	

New Zealand site of batch release

Name of release site	Pfizer New Zealand Limited
Street address of batch release site	Level 1, Suite 1.4, Building B 8 Nugent Street Grafton Auckland 1023

8. Provided information

Documentation (Please ensure ALL relevant sections in this table are completed)	**Section**	**Volumes(s)**
If available, electronic dossier (two copies, hyperlinked, and copy-enabled) should be provided. [Sponsor comment]: Note, as agreed with Medsafe at the pre-submission meeting held 24 September 2020, this application is provided in eCTD format only and will be submitted on a rolling basis.		
Module 1	-	Provided in electronic version only
• Detailed table of contents for the dossier	N/A	Provided in electronic version only
• Labels	1.3.3	
• Data sheet	1.3.1	
• Package Insert	1.3.1.4	
• GMP documentation	1.11.4	
• CEP with declaration of access	N/A	N/A
Abbreviated process documentation	N/A	N/A
• Detailed table of the overseas regulatory history	N/A	
• Evaluation reports from overseas regulatory authorities	N/A	
• Company responses to issues raised and evaluation of the responses by overseas regulatory authorities	N/A	
• Overseas approval details (approval letter, specifications)	N/A	
CTD Module 2 Overviews and Summaries	-	Provided in electronic version only
CTD Module 3, or, for lower risk medicines, EU Part II Chemical, pharmaceutical and/or biological documentation	-	Provided in electronic version only
• Drug product formulation/Batch formula	3.2.P.1 / 3.2.P.3.2	
• Drug product release and expiry specifications	3.2.P.5.1	
• Proprietary ingredients formulation	N/A	N/A
CTD Module 4 Toxicological and pharmacological (pre-clinical) documentation	-	Provided in electronic version only
CTD Module 5 Clinical Documentation	-	Provided in electronic version only
• Bioequivalence study results	N/A	N/A
• Bridging study between the reference product used in the biostudy and the New Zealand reference product	N/A	N/A
• Bioanalytical method validation	5.3.1.4	Provided in electronic version only

Drug Master File(s) or Plasma Master File(s)	N/A	N/A
Letter(s) of access to the Drug Master File(s) or Plasma Master File(s)	N/A	N/A
Total number of volumes submitted:	-	1 x electronic dossier in eCTD format

Medsafe assessment report

Title	**Cominarty /Tozinameran/ BNT162b6, concentrated suspension for injection, 30 µg/0.3 mL, 0.45 mL multi-dose vial – Risk Management Plan**	
Active ingredient	**Product name**	**Sponsor**
COVID-19 mRNA Vaccine	Cominarty	Pfizer
	RFI questions and responses	

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[redacted]

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[redacted]

5 PUBLIC SUMMARY

Summary of risk management plan for Comirnaty.

This is a summary of the risk management plan (RMP) for Comirnaty. The RMP details important risks of Comirnaty, how these risks can be minimised, and how more information will be obtained about Comirnaty's risks and uncertainties (missing information).

Comirnaty's data sheet and its Consumer Medicine information give essential information to healthcare professionals and patients on how Comirnaty should be used.

This summary of the RMP for Comirnaty should be read in the context of all this.

Important new concerns or changes to the current ones will be included in updates of Comirnaty's RMP.

I. The Medicine and What It Is Used For

Comirnaty is a vaccine for active immunisation to prevent COVID-19 disease caused by SARS-CoV-2 virus, in individuals 16 years of age and older. (see data sheet for the full indication). It contains Nucleoside-modRNA encapsulated in lipid nanoparticles as the active substance and it is given intramuscularly.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Comirnaty, together with measures to minimise such risks and the proposed studies for learning more about Comirnaty's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the CMI and data sheet addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Comirnaty is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Comirnaty are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as

identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Comirnaty. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 7: list of Important Risks and Missing Information

Important identified risks	None
Important potential risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and lactation
	Vaccine effectiveness

II.B Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference.

Table 8: Important Potential Risk

Evidence for linking the risk to the medicine	VAED is considered a potential risk because it has not been seen in human studies with this or other COVID-19 vaccines being studied. It has not been seen in vaccine studies in animal models of the SARS-CoV-2 virus either. However, in selected vaccine studies in animal models as well as in some laboratory studies in animal cells infected with 2 other related coronaviruses (SARS-CoV-1 and MERS-CoV), abnormalities in immune responses or cellular responses indicative of VAED were observed. Because of this, VAED is considered a potential risk. In the past there have been other examples of particularly respiratory viruses where VAED has been observed. For example, some children who received an inactivated respiratory syncytial virus vaccine (a different type of virus), had worse signs of disease when they were subsequently infected with respiratory syncytial virus. VAED is thought to occur by several mechanisms where the immune response is not fully protective and actually either causes the body to have an inflammatory reaction due to the type of immune response with specific types of T-cells, or the body does not produce enough strong antibodies to prevent SARS-CoV-2 infection of cells or produces weak antibodies that actually bind to the virus and help it to enter cells more easily, leading to worse signs of disease.
Risk factors and risk groups	It is thought that the potential risk of VAED may be increased in individuals producing a weak antibody response or in individuals with decreasing immunity over time.
Risk minimisation measures	Routine risk minimisation measures None. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: C4591001 C4591008 C4591010 C4591011 C4591012 ACCESS/VAC4EU See section II.C of this summary for an overview of the post-authorisation development plan.

Table 9: Missing information use in pregnancy and lactation

Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6; PL section 2 Additional risk minimisation measures: No risk minimisation measures.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: C4591008 C4591011 C4591012 C4591015 See section II.C of this summary for an overview of the post-authorisation development plan.

Table 10: Missing information vaccine effectiveness

Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4 and 5.1. Additional risk minimisation measures: No risk minimisation measures.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: C4591014 BNT162-01 Cohort 13 See section II.C of this summary for an overview of the post-authorisation development plan.

Table 11: Studies in Post-authorisation development plan

Study	Purpose of the study
C4591001	The objective of the study is to evaluate the safety, tolerability, immunogenicity and efficacy of COVID-19 mRNA vaccine. An unfavorable imbalance between the vaccine and control groups in the frequency of COVID-19 disease, in particular for severe COVID-19 disease, may suggest the occurrence of vaccine associated enhanced disease. Surveillance is planned for 2 years following Dose 2.
C4591008	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 disease in real-world use of COVID-19 mRNA vaccine.
C4591011	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 disease in a cohort of people within the Department of Defense Healthcare System.
C4591012	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 disease in real-world use of COVID-19 mRNA vaccine.
C4591010	Assessment of occurrence of safety events, including severe or atypical COVID-19 disease in real-world use of COVID-19 mRNA vaccine.
C4591015	Planned clinical study to assess safety and immunogenicity in pregnant women who receive COVID-19 mRNA vaccine. Safety and immunogenicity of COVID-19 mRNA vaccine in pregnant women.
C4591014	Estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against potential COVID-19 illness requiring admission to the ED or hospital where SARS-CoV-2 is identified.
BNT162-01 Cohort 13	To assess potentially protective immune responses in immunocompromised adults.
ACCESS/ VAC4EU	Not available.

6 DISCUSSION AND CONCLUSIONS

It is considered that the safety specification for this product is currently inadequate and does not accurately reflect the important known risks, important potential risks or missing information. The RMP should be updated to include the additional risks and state how the missing information will be addressed. The additional studies appear to generally address the information gaps, but the company should state specifically how they will provide information on the NZ concerns raised above and listed at the beginning. In addition the provision of the results of these studies and provision of safety updates should be made a condition of approval.

Attachment 3 – RNA sequence

Figure 3.2.S.1.2-3. RNA nucleotide Sequence of the BNT162b2 drug substance:

Nucleotide sequence 5'→3':

```
GAGAAYAAAC YAGYAYYCYY CYGGYCCCCA CAGACYCAGA GAGAACCCGC 50
CACCAYGYYC GYGYYCCYGG YGCYGCYGCC YCYGGYGYCC AGCCAGYGYG 100
YGAACCYGAC CACCAGAACA CAGCYGCCYC CAGCCYACAC CAACAGCYYY 150
ACCAGAGGCG YGYACYACCC CGACAAGGYG YYCAGAYCCA GCGYGCYGCA 200
CYCYACCCAG GACCYGYYCC YGCCYYYCYY CAGCAACGYG ACCYGGYYCC 250
ACGCCAYCCA CGYGYCCGGC ACCAAYGGCA CCAAGAGAYY CGACAACCCC 300
GYGCYGCCCY YCAACGACGG GGYGYACYYY GCCAGCACCG AGAAGYCCAA 350
CAYCAYCAGA GGCYGGAYCY YCGGCACCAC ACYGGACAGC AAGACCCAGA 400
GCCYGCYGAY CGYGAACAAC GCCACCAACG YGGYCAYCAA AGYGYGCGAG 450
YYCCAGYYCY GCAACGACCC CYYCCYGGGC GYCYACYACC ACAAGAACAA 500
CAAGAGCYGG AYGGAAAGCG AGYYCCGGGY GYACAGCAGC GCCAACAACY 550
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CAGGGCAACY YCAAGAACCY GCGCGAGYYC GYGYYYAAGA ACAYCGACGG 650
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CYYCGYGAYC CGGGGAGAYG AAGYGCGGCA GAYYGCCCCY GGACAGACAG 1300
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CCCYGGCACC AACACCAGCA AYCAGGYGGC AGYGCYGYAC CAGGACGYGA 1900
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CYGCYAGYYC CAGACACCYC CCAAGCACGC AGCAAYGCAG CYCAAAACGC 4050
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AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAA 4284
```

Sequence length: 4284, which includes G to denote the presence of the 5'-cap analog
G: 1062 C: 1315 A: 1106 Y: 801
A = Adenine; C = Cytosine; G = Guanine; Y = N1-methylpseudouridine