



EMA/CHMP/21199/2024
Committee for Medicinal Products for Human Use (CHMP)

Type II variation assessment report

Procedure No. EMEA/H/C/005735/II/0202

Invented name: COMIRNATY

Common name: COVID-19 mRNA vaccine (nucleoside-modified)

Marketing authorisation holder (MAH): BioNTech Manufacturing GmbH

This application is in the area of: Quality

eCTD sequences related to the procedure: 0598, 0605, 0613



Status of this report and steps taken for the assessment			
Current step	Description	Planned date	Actual Date
☐	Start of procedure	27 Dec 2023	27 Dec 2023
☐	CHMP Rapporteur Assessment Report	15 Jan 2024	15 Jan 2024
☐	CHMP members comments	17 Jan 2024	17 Jan 2024
☐	Updated CHMP Rapporteur Assessment Report	19 Jan 2024	19 Jan 2024
☐	Start of written procedure	23 Jan 2024	23 Jan 2024
☐	Request for Supplementary Information	25 Jan 2024	25 Jan 2024
☐	Submission of Responses	30 Jan 2024	30 Jan 2024
☐	Re-start of procedure	31 Jan 2024	31 Jan 2024
☐	CHMP Rapporteur Assessment Report	14 Feb 2024	12 Feb 2024
☐	CHMP members comments	19 Feb 2024	19 Feb 2024
☐	Updated CHMP Rapporteur Assessment Report	22 Feb 2024	22 Feb 2024
☐	Start of written procedure	27 Feb 2024	27 Feb 2024
☒	Opinion	29 Feb 2024	29 Feb 2024

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Declarations

This application includes an Active Substance Master File (ASMF):

☐ Yes ☒ No

☒ The assessor confirms that proprietary information on, or reference to, third parties (e.g. ASMF holder) or products are not included in this assessment, including in the Product Information, if any, unless there are previous contracts and/or agreements with the third party(ies).

Whenever the above box is un-ticked please indicate section and page where confidential information is located here:

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, BioNTech Manufacturing GmbH submitted to the European Medicines Agency on 15 December 2023 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
B.I.z	B.I.z - Quality change - Active substance - Other variation	Type II	None

Type II, B.I.z, To update the information in Module 3.2.S.2.3 to provide additional information for sequence elements in the plasmid DNAs used in the manufacturing process of the active substances Tozinameran, Riltozinameran, Famtozinameran and Raxtozinameran, to present a risk assessment regarding residual DNA that may be present in the vaccine, and to provide results of studies to further quantitate and characterise the residual DNA in the vaccine of multiple lots/variants/sites.

The requested variation proposed no amendments to the Product Information.

2. Overall conclusion and impact on the benefit/risk balance

The Applicant has submitted a variation applicable to provide additional information for sequence elements in the plasmid DNAs used in the Comirnaty Original, B.1.1.529, BA.4/BA.5 and XBB.1.5. Circular Plasmid DNA and its derivative - Linear DNA template, used as starting material in BNT162b2 DS manufacture.

Originally, information on the sequence elements encoded in the plasmid DNA starting material presented in the dossier was focused solely on the functional elements (T7 promoter, 5' and 3' UTR, ribosome binding site, cloned version of the Spike gene, linearization site, genes conferring kanamycin resistance and plasmid origin of replication), since those are utilized for the manufacture of Comirnaty Drug Substances and their corresponding Linear DNA templates. However, the above-mentioned plasmid DNA starting materials also contain additional sequence elements, which are not utilized for the BNT162b2 DS manufacture, and therefore have not been previously annotated in the dossier. These elements are derived from the backbone of the cloning vector originally used for the generation of plasmid DNA constructs for Comirnaty and include the SV40 sequence elements (SV40 PolyA signal, SV40 Promoter/Enhancer, including SV40 Origin), f1 Origin and TK PolyA terminator. As requested in previous communication with the MAH, data on the origin/source, location and hypothetical function of those elements are now provided in all relevant sections of the dossier.

A safety risk assessment was conducted regarding residual DNA that may be present in the vaccine. The assessment is based on consideration of the whole manufacturing process, characterization data obtained from the residual DNA, as well as on extensive information regarding the potential risks posed by residual DNA or plasmids. The specific questions addressed relate to the possible safety risks posed to vaccinees by the residual DNA in general and by the non-utilized sequence elements (SV40-derived elements).

Several key points were considered when performing the risk assessment and it is agreed that the likelihood of any residual DNA integrating into human genome is regarded as negligible.

The SV40-derived sequences comprise a small fraction of the total residual DNA of Comirnaty and are included in the overall risk assessment. The properties of each sequence element are well known, and the functional roles have been now documented in relevant sections of the dossier. Current scientific knowledge, reviewed in the risk assessment, confirm that none of these elements facilitates chromosomal integration, nor do they contribute to the persistence or replication of the plasmid in the human body. No SV40 proteins are encoded or present in the vaccine. Moreover, the SV40 sequence elements are not oncogenes and do not cause cancer.

Therefore, it is in general agreed that the presence of residual DNA in Comirnaty, at levels below the approved limits, and the possible presence of the non-utilized SV40-derived sequence elements in the residual DNA do not alter the overall safety profile of the vaccine and does not pose a risk to vaccinees.

In response to RSI, additional characterization data were provided by the MAH to further support this conclusion. These studies include analysis of the size distribution of the residual DNA template, qualitative and quantitative analysis of the SV40 elements in the residual DNA and DNA plasmid replication analysis in bacteria. Evaluation of 236 batches manufactured between 2020 and 2023 at three commercial manufacturing sites (Pfizer Global Supply (PGS) Andover, PGS Grange Castle, and BioNTech Marburg) and encompassing four unique variants (Wildtype/Original and Omicron BA.1, BA.4/BA.5, and XBB.1.5) demonstrates that residual DNA template results are similar across manufacturing sites and comply with established specifications. Rapporteur's conclusion is that no update to the provided risk assessment is needed based on the additional characterization of residual DNA in the vaccine and that there is no evidence to support a potential risk of residual plasmid sequence accumulation in cells exposed to residual plasmid DNA.

The applicant also stated that the feasibility of removal of the non-utilized sequence elements from the plasmid DNA starting material is currently under evaluation. This approach was endorsed by BWP, however any outcome of this investigation will be dealt with outside the framework of this procedure, i.e. as part of the life-cycle management.

In conclusion, the Comirnaty variation EMEA/H/C/005735/II/202 is recommended for approval.

The benefit-risk balance of Comirnaty, remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		Type	Annexes affected
B.I.z	B.I.z - Quality change - Active substance - Other variation	Type II	None

☒ is recommended for approval.

Amendments to the marketing authorisation

The variation leads to no amendments to the terms of the Community Marketing Authorisation.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Not applicable

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