QUERY 1

In order to further support the conclusions of the provided risk assessment, results from the ongoing characterization analysis regarding the residual DNA in the vaccine of multiple lots/variants/sites should be submitted for evaluation.

RESPONSE 1

In support of the variation, the following response provides additional information of Comirnaty (BNT162b2) variant Circular plasmid DNA and Linear DNA template starting material and the corresponding residual DNA within the Drug Substance. These characterization activities are provided in the technical report INX100594280.

The residual DNA template characterization activities, which included samples from multiple lots, variants and manufacturing sites, have been completed and encompass the following assessments:

- The analysis and characterization of the size and distribution of residual DNA template fragments by TapeStation Electrophoresis.
- The assessment of the presence of SV40 CCI [redacted] sequence elements in residual DNA template fragments using polymerase chain reaction (PCR) based assay.
- CCI [redacted] CCI [redacted]

It is considered that additional characterization of residual DNA in the vaccine conducted at the request of Health Authorities does not change the outcome of this risk assessment. Therefore, a further update of the risk assessment is not needed.

Refer to technical report INX100594280 for further details of the additional characterization analysis.

Literature References

None

SUPPORTING DOCUMENTATION

New or Replaced Supporting Documentation

INX100594280

Previously Submitted Supporting Documentation

None

090177e19fc957cd\Approved\Approved On: 29-Jan-2024 14:58 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
Data up to date as of 9 February 2024

QUERY 2

The applicant is asked to clarify and discuss based on scientific literature, whether presence of the SV40 CCI in residual plasmid sequences could give rise to amplification of these plasmid sequences in the nucleus of eukaryotic cells in absence of the SV40 Tag. If this is considered possible, the risk of residual plasmid sequence accumulation in cells taken up residual plasmid DNA should be discussed.

RESPONSE 2

According to published literature, the large T-antigen and to a lesser extent the small t-antigen are absolutely required for SV40 CCI -based DNA syntheses initiation and replication (Parsons et al., 1990; Butel and Lednicky, 1999; Kelly, 1988). The large T-antigen is not present in the Comirnaty plasmid DNA. Since the large T-antigen is only expressed in the full SV40 genome, it is not present in non-SV40 infected cells.

A search of the literature using the term "SV 40 replication in the absence of large T-antigen" yielded no results. Therefore, in addition to the low probability of the SV40 CCI sequence becoming incorporated into genomic DNA and the rapid degradation of any low level residual DNA (reference is made to the residual DNA risk assessment), in the absence of large T-antigen, there cannot be DNA amplification / replication.

Therefore, there is no evidence to support a potential risk of residual plasmid sequence accumulation in cells exposed to residual plasmid DNA.

Literature References

J S Butel, J A Lednicky. Cell and molecular biology of simian virus 40: implications for human infections and disease. J Natl Cancer Inst. 1999 Jan 20;91(2):119-34. DOI: 10.1093/jnci/91.2.119.

Thomas J. Kelly. SV40 DNA Replication. The Journal of Biological Chemistry, Vol. 263 No. 34 Issue of December 5, pp. 17889-17892,1988. The American Society of Biochemistry and Molecular Biology. Inc

R Parsons, M E Anderson, P Tegtmeyer. Three domains in the simian virus 40 core origin orchestrate the binding, melting, and DNA helicase activities of T antigen. J Virol. 1990 Feb;64(2):509-18. DOI: 10.1128/JVI.64.2.509-518.1990.

SUPPORTING DOCUMENTATION

New or Replaced Supporting Documentation

None

Previously Submitted Supporting Documentation

BNT162b2 Residual DNA Risk Assessment, sequence 0598.

090177e19fc957cd\Approved\Approved On: 29-Jan-2024 14:58 (GMT)
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof
ema.europa.eu
Data up to date as of 20 February 2024