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## Toxicology Review of SPIKEVAX (mRNA-1273 COVID-19 Vaccine)

BLA 125752/0

Type and date of submission: Original; May 28, 2021

Sponsor: Moderna TX, Inc.

Product: SPIKEVAX (mRNA-1273 COVID-19 vaccine)

Related/referred products: IND 19745, IND 19365, EUA 27073 and MF (b) (4)

Proposed indication for use: Active immunization to induce protective immunity against acute respiratory disease associated with the SARS-COV-2 virus

Reviewer: (b) (6) (b) (6)

### Précis

The sponsor submitted 14 toxicity study reports. Six toxicity study reports of 5 similar mRNA constructs, one genotoxicity study of (b) (4) mRNA in SM-102 containing LNP, one genotoxicity study report of (b) (4) mRNA in SM-102 containing LNP and two genotoxicity study reports of its inactive ingredient (SM-102) were submitted previously in other INDs/MF and had been reviewed in their respective applications as follow:

- (1) 1-month intramuscular injection toxicity study of (b) (4) in rats (study # 5002045 in MF (b) (4))
- (2) 1-month intramuscular injection vaccine study of (b) (4) in rats (study #5002231 in MF (b) (4))
- (3) 6-week intramuscular injection toxicity study of (b) (4) in rats (study #5002034 in IND (b) (4))
- (4) 6-week intramuscular injection toxicity study of (b) (4) in rats (study #5002158 in IND (b) (4))
- (5) 1-month intramuscular injection toxicity study of (b) (4) in rats (study #5002400 in IND (b) (4))
- (6) 1-month study of (b) (4) by intramuscular injection in rats (study #5002033 in IND (b) (4))
- (7) (b) (4) mRNA: Mammalian erythrocyte micronucleus test in rats (study #9800399 in INDs (b) (4) and (b) (4))
- (8) SM-102 Bacterial reverse mutation test (study # 9601567 in MF (b) (4))
- (9) SM-102 In vitro mammalian micronucleus test (study #9601568 in MF (b) (4))
- (10) In vivo rat micronucleus assay of (b) (4) mRNA in SM-102 containing LNP (Study #AF878FU.125012NNGLPICHBTL in IND (b) (4))

Two toxicity study reports of the vaccine (mRNA-1273) were submitted in IND 19745 and had been reviewed as follow:

- (11) Non-GLP intramuscular toxicity study of mRNA-1273 in rats (study #2308-123)
- (12) Intramuscular combined developmental and prenatal/postnatal reproductive toxicity study report of mRNA-1273 in rats (Study #20248897)

Two genotoxicity study reports of a bacterial reverse mutation test (study # 96010350) and an in vitro mammalian cell micronucleus test (study # 9601036) of its inactive ingredients (PEG2K-DMG) and (b) (4) are hereby reviewed, and their study results are summarized below:

In the in vitro mammalian cell micronucleus test conducted in Feb-July 2015, (b) (4)



In the bacterial reverse mutation test conducted in February-July 2015, (b) (4)



#### Conclusion and recommendation

The safety of the vaccine is supported by the aggregate rat repeat-dose toxicity profile observed in six GLP toxicity studies of (b) (4) vaccines formulated in SM-102-containing LNP encoded by various antigens (mRNAs) and the mRNA-1273 data of a non-GLP toxicity study with limited parameters monitored. All genotoxicity study reports indicate no genotoxic effect of its inactive ingredients (SM-102 and PEG2K-DMG). It can be concluded from the developmental toxicity study in female rats that mRNA1273 given prior to mating and during gestation periods at dose of 100 ug did not have any effects on female fertility, fetal/embryonal development, and postnatal developmental effects.

The application is approvable from a toxicological perspective. The animal developmental toxicity study data could be indicated in the labeling as recommended below:

### 8.1 Pregnancy

#### Risk Summary

A developmental toxicity study has been performed in female rats administered a single human dose of SPIKEVAX (100ug) twice prior to mating and twice during gestation. The study revealed no evidence of harms to the fetuses [see 8.1 Animal Data].

#### Animal data

In a developmental toxicity study, the effect of SPIKEVAX was evaluated in pregnant rats. Animals were administered a single human dose of SPIKEVAX (100ug) by the intramuscular route on four occasions: 28 and 14 days prior to mating, and on gestation days 1 and 13. No vaccine-related fetal malformations or variations and no adverse effects on postnatal development were observed in the study.

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

SPIKEVAX has not been evaluated for carcinogenic or mutagenic potential, or male infertility in animals. SPIKEVAX did not affect female fertility in a rat developmental toxicity study [see Pregnancy (8.1)].

Concurrence: (b) (6) (b) (6)