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3.2.P.5.5 CHARACTERIZATION OF IMPURITIES

The impurity profile of mRNA-1273 Drug Product is the same as that of the mRNA-1273 Lipid Nanoparticle (LNP), with the exception of potential extractables/leachables, no additional impurities are anticipated to form or be introduced during mRNA-1273 Drug Product manufacturing. Each of the impurities discussed in Section 3.2.S.3.2 {CX-024414}, [redacted], and Section 3.2.S.3.2 {mRNA-1273 LNP}, is present in the mRNA-1273 Drug Product. An evaluation of potential extractables and leachables is provided in the following section.

3.2.P.5.5.1 Extractables and Leachables

The potential extractables and leachables from manufacturing components and container closure systems were evaluated for all materials with liquid product contact used in mRNA-1273 Drug Product production process, with the exception of the following:

- Stainless steel equipment, reusable flex lines, gaskets, and O-rings, as these components are assessed as part of equipment qualification activities.
- Single-use components for weighing and dispensing raw materials, as these are typically short contact duration, not exposed to product, and have very low contact area.

3.2.P.5.5.1.1 Risk Assessment

A systematic risk assessment was performed in alignment with the [redacted] for evaluating extractables and leachables in biopharmaceutical manufacturing systems. An overall leachable risk rating (LRR) was calculated for each material as a weighted sum of the following risk parameters:

- **Distance along the process stream**: the position of a component in the production process has an impact on the likelihood of clearance of leached compounds. Risk rating increases closer to final product storage.
- **Exposure temperature**: higher temperatures may increase the possibility of leachable migrating into the process stream.
- **Exposure duration**: the length of exposure may increase the propensity for leaching.
- **Process fluid interaction**: the composition of the process fluid may impact the propensity of leaching. Risk rating increases with increasing organic content, surfactant concentrations, and pH extremes.
- **Dilution ratio**: the concentration of leachable in the process stream is dependent on both the amount of leachable that migrate into the process stream and the volume of liquid the polymeric component is exposed to. Higher surface areas provide more opportunity of leaching, whereas lower process volumes concentrate the leachable and represent an increased risk.

The resulting LRR determined the risk mitigation actions, as summarized in Table 1. The medium- and high-risk materials for each manufacturing process are summarized in the following sections. Note that the same component may have different ratings depending on the conditions of a given manufacturing operation; the highest score is represented in the following sections. Low risk items are not discussed.

Table 1: LRR Risk Mitigation Actions

[redacted]

3.2.P.5.5.1.2 mRNA-1273 Drug Product Manufacturing Process (Scale A)

The materials in Table 2 and Table 3 were designated as medium and high-risk during the risk assessment, respectively. Actions for risk mitigation as described in Table 1 for medium risk materials have been completed. In the case of the high-risk materials in Table 3, vendor-generated extractables data was used to perform an initial quantitative toxicological assessment. None of the materials was identified to pose a safety risk to humans at the levels assessed for the mRNA-1273 Drug Product. Further product-specific simulated leachables study on these components has been initiated.

Table 2: Medium Risk Consumables for mRNA-1273 Drug Product Manufacturing Process Scale A

[redacted]

Table 3: High Risk Consumables for mRNA-1273 Drug Product Manufacturing Process Scale A

[redacted]

3.2.P.5.5.1.3 mRNA-1273 Drug Product Manufacturing Process (Scale B)

The materials in Table 4 and Table 5 were designated as medium and high-risk during the risk assessment, respectively. Actions for risk mitigation as described in Table 1 for medium risk materials are completed. In the case of the high-risk container closure components in Table 5, vendor-generated extractables data was used to perform an initial quantitative toxicological assessment. None of the materials was identified to pose a safety risk to humans at the levels assessed for the mRNA-1273 Drug Product. Further product-specific simulated leachables study on these components has been initiated. Actions for risk mitigation of high-risk process consumables are ongoing and will be reported as available.

Table 4: Medium Risk Consumables for mRNA-1273 Drug Product Manufacturing Process Scale B

[redacted]

Table 5: High Risk Consumables for mRNA-1273 Drug Product Manufacturing Process Catalent Scale B

[redacted]