

3.2.A.2. ADVENTITIOUS AGENTS SAFETY EVALUATION [BNT MAINZ AND RENTSCHLER]

Multiple mechanisms, procedures, and assays are used to minimize the entry of adventitious agents into the process stream and detect those agents that do enter the process stream. The adventitious agent control program includes the engineering systems of the facility and vessels, the control of the raw materials used in the process, various filtration steps to control microbial load in buffers and the process stream, and in-process and environmental testing to monitor the level of adventitious agents in and around the process stream.

3.2.A.2.1. Introduction

The main theoretical risk associated with these ingredients is contamination of the product by Transmissible Spongiform Encephalopathy (TSE) agents. A multifaceted program exists to ensure the viral safety of the drug substance, including development of a purification process and formulation that are devoid of human or animal derived components.

Management of transmissible spongiform encephalopathy (TSE) / bovine spongiform encephalopathy (BSE) risks is part of the comprehensive adventitious agent control program for BNT162b2 drug substance.

All raw materials used in the production of drug substance are evaluated as part of a comprehensive program to identify and manage TSE/BSE risks. Under this program, the risk of transmission of TSE/BSE from animal-derived materials is managed by sourcing such materials in a manner consistent with the current industry guidelines including those from the European Medicines Agency (EMA), the Therapeutic Goods Administration (TGA), and the World Health Organization (WHO).

The conclusion from the TSE/BSE risk evaluations performed for raw materials in the BNT162b2 process is that the risk of transmitting TSE/BSE via drug substance has been minimized.

Details of any starting material, reagent or component containing material of animal origin including its source and preparation are discussed in the following sections. These products are commercially available and are not specially produced for the applicant.

Other materials of animal origin may be used in the production of polymer for filters, manifolds, containers, and/or filter components. These equipment components may contain traces of animal tallow derivatives. The tallow is processed under rigorous conditions and is considered compliant with the TSE note for guidance (EMA/410/01).

Moreover, equipment and materials are cleaned, sterilized and/or chemically decontaminated according to validated procedures.

3.2.A.2.2. Non-Viral Adventitious Agents

3.2.A.2.2.1. Raw Material Sourcing and Testing

Raw material information is provided in Section 3.2.S.2.3 Materials Used in Manufacture.

Information for animal-derived materials is provided in Table 3.2.A.2-1. All other materials are of synthetic and/or biological origin.

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Table 3.2.A.2-1. Materials of Animal Origin Used in the Manufacture of BNT162b2 Drug Substance

Raw Material (Source ^a)	Manufacturing Process Stage (Use)	Country of Origin ^b	Comment (Certificate of Suitability availability, other significant safety details)
	Drug substance manufacturing	Germany	Based on information provided by manufacturer [REDACTED] [REDACTED] was manufactured without any animal or human materials, or cell culture material derived from any TSE relevant animal species, according to EMA/410/01 Rev. 3. [REDACTED] reports that the [REDACTED] purification process utilizes a chromatographic column that contains [REDACTED]. As indicated by [REDACTED] in the Notices from European Union Institutions, Bodies, Offices and Agencies' "Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products" (EMA/410/01 rev.3) (2011/C 73/01), Section 2. SCOPE clarifies that "Pigs and birds, which are animal species of particular interest for the production of medicinal products, are not naturally susceptible to infection via the oral route. Therefore they are not TSE-relevant animal species within the meaning of this Note for Guidance."
Filters of various sizes	Drug substance manufacturing	Not available	The materials of construction of these filters are not of direct animal origin. However, some raw materials present in the filter case may contain traces of stearate materials, derived from animal tallow. The vendor data confirms that the tallow derivatives meet the requirements of the current guidance which gives specific consideration to tallow derivatives and states that they are unlikely to be infectious if processed under rigorous conditions.
Flexible containers (Bag systems) used at various processing steps and to hold final drug substance	Drug substance manufacturing	Not available	The containers (Bag systems) do not contain any substances derived from direct animal sources. Some raw materials present in the Bag systems include stearate stabilizers (Ca or Zn Stearates) and/or other additives derived from tallow. The vendor data confirms that the tallow derivatives meet the requirements of the current guidance which gives specific consideration to tallow derivatives and states that they are unlikely to be infectious if processed under rigorous conditions.

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Raw Material (Source ^a)	Manufacturing Process Stage (Use)	Country of Origin ^b	Comment (Certificate of Suitability availability, other significant safety details)
Clear C-flex tubing, various sizes, including manifold assemblies provided by vendors	Drug substance manufacturing	Not available	The materials of construction of these manifold and tubing assemblies are not of direct animal origin. Some raw materials present in Clear C-flex tubing, including manifold assemblies include stearate stabilizers (Ca or Zn Stearates) and/or other additives derived from tallow. The vendor data confirms that the tallow derivatives meet the requirements of the current guidance which gives specific consideration to tallow derivatives and states that they are unlikely to be infectious if processed under rigorous conditions.
Tubing assembly	Drug substance manufacturing	Porcine and bovine tallow sourced from Canada, Mexico, USA	The materials of construction of these tubing assemblies are not of direct animal origin. However, polypropylene used in the filter case may contain traces of stearate materials, derived from animal tallow. The polypropylene meets the requirements of the current guidance which gives specific consideration to tallow derivatives and states that they are unlikely to be infectious if processed under rigorous conditions.

a. Source as defined in supplier documentation.

b. Countries of origin as defined in supplier documentation.

3.2.A.2.3. Conclusion

In summary, a comprehensive, multifaceted program is in place to ensure that the risk, with respect to potential viral and non-viral adventitious agent contamination of drug substance, is acceptable.

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