TABLE OF CONTENTS

LIST OF TABLES 1

LIST OF FIGURES 1

3.2.P.3.4. CONTROL OF CRITICAL STEPS AND INTERMEDIATES – DRUG PRODUCT INTERMEDIATE 0.5 MG/ML – TRIS/SUCROSE – CONTAINER CLOSURE SYSTEM 2

3.2.P.3.4.1. [redacted] Containers 2

3.2.P.3.4.1.1. Description of Container Closure System 2

3.2.P.3.4.1.2. Suitability and/or Safety of the Container Closure System 3

3.2.P.3.4.1.3. Extractables 5

3.2.P.3.4.1.4. Leachables 7

LIST OF TABLES

Table 3.2.P.3.4-1. [redacted] Film Extraction Study Results and Calculated TDI 6

LIST OF FIGURES

Figure 3.2.P.3.4-1. [redacted] Container Schematic Drawing 3

Figure 3.2.P.3.4-2. Construction of [redacted] Container 4

3.2.P.3.4. CONTROL OF CRITICAL STEPS AND INTERMEDIATES – DRUG PRODUCT INTERMEDIATE 0.5 MG/ML – TRIS/SUCROSE – CONTAINER CLOSURE SYSTEM

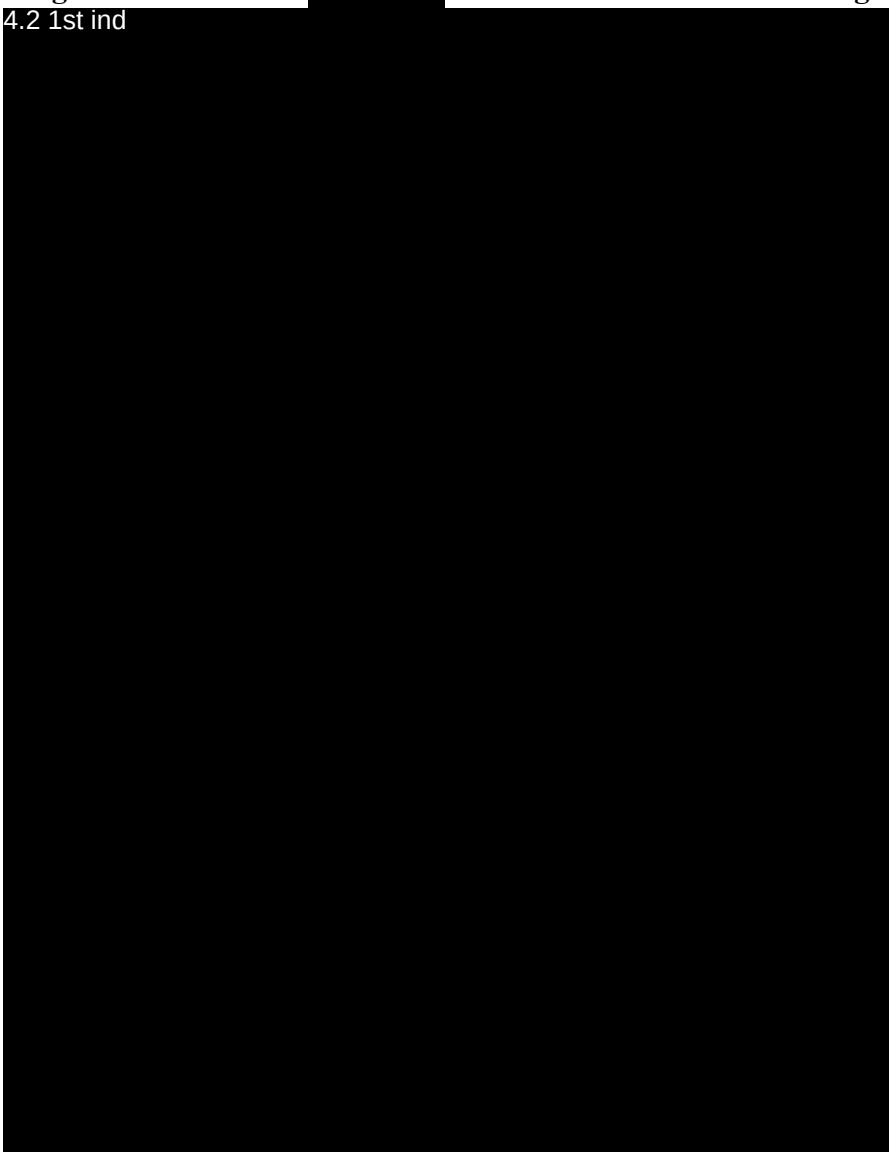
3.2.P.3.4.1. [redacted] Containers

The Tris/Sucrose Drug Product Intermediate (DPI) is filled into [redacted] containers, [redacted], and stored frozen. The terms FFT "container" or "bag" are also interchangeably used to describe the [redacted] containers.

3.2.P.3.4.1.1. Description of Container Closure System

[redacted] containers are sterile, single-use, flexible, disposable bags specifically designed for freezing, thawing and frozen storage of biopharmaceuticals. A schematic drawing of the [redacted] container is presented in Figure 3.2.P.3.4-1.

Figure 3.2.P.3.4-1. 4.2 1st ind Container Schematic Drawing



3.2.P.3.4.1.2. Suitability and/or Safety of the Container Closure System

4.2 1st ind was chosen as the material of construction because it is suitable for freezing and storage of the DPI. 4.2 1st ind containers have acceptable physical properties and thermal resistance over a wide temperature range. 4.2 1st ind containers also have an acceptable chemical resistance and provide a suitable contact surface for long-term storage of the DPI in the frozen form. The containers are designed and qualified to appropriately protect the DPI from the environment throughout storage.

Figure 3.2.P.3.4-2. Construction of 4.2 1st ind Container

The physicochemical properties of the 4.2 1st ind contact layer have been tested in compliance with the recommendation of Ph. Eur. 3.1.7 Ethylene-Vinyl Acetate Copolymer for Containers and Tubing for Parenteral Nutrition Preparations and USP <661> Containers, Physicochemical Tests-Plastics. Biocompatibility tests have been performed by the vendor to demonstrate that all components used for manufacture are biocompatible and meet or exceed the current USP <87>, USP <88> and ISO 10993 requirements on "Biological Evaluation of Medical Devices".

The 4.2 1st ind containers are accepted on the basis of the supplier's Certificate of Analysis (COA) or Certificate of Conformance (COC). Container integrity is confirmed visually at the point of use.

The compatibility of the Tris/Sucrose DPI with the containers is evaluated through studies of DPI stability in 4.2 1st ind containers (Section 3.2.P.3.4 Control of Critical Steps and Intermediates – Drug Product Intermediate 0.5 mg/ml – Stability Summary and Conclusion – Tris/Sucrose). Stability data obtained to date support container closure compatibility for up to 3 months at recommended long term storage condition (-90 to -60 °C) and short term storage 4.2 1st ind within the current 3 months shelf life.

3.2.P.3.4.1.3. Extractables

A controlled extraction study performed on the 4.2 1st ind container film was used to establish a qualitative and quantitative extractable profile. The study was performed using model solvents that varied in pH and solvent strength. The series of extraction solutions used are listed below:

4.2 1st ind

4.2 1st ind

4.2 1st ind

4.2 1st ind

4.2 1st ind

4.2 1st ind

Table 3.2.P.3.4-1. 4.2 1st ind **Film Extraction Study Results and Calculated TDI**

Compound	Extraction Solvent	Analysis Technique	Highest Concentration µg/mL	TDI µg/day
4.2 1st ind				

4.2 1st ind

3.2.P.3.4.1.4. Leachables

The leachables safety profile of the [redacted] container was assessed [redacted]

[redacted]

[redacted]

[i] Ball D, Blanchard J, Jacobson-Kram D, et al. Development of safety qualification thresholds and their use in orally inhaled and nasal drug product evaluation. Toxicol Sci 2007; 97(2):226-362