MODULE 1.5.1: BIOWAIVER JUSTIFICATION REPORT

Product: Poly-Zinc-Liothyronine (PZL) 25 μg Sustained-Release Depot

Submission Type: Category 1 (New Dosage Form)

Reference Product: Cytomel® (Liothyronine Sodium) 25 μg Tablets

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1. REQUEST FOR WAIVER

In accordance with **EMA Guideline CPMP/EWP/QWP/1401/98** and **TGA ARGPM Guidance**, the Sponsor (Georgios Sopasis) requests a waiver of the requirement for a full Phase III clinical efficacy study for the proposed Poly-Zinc-Liothyronine (PZL) depot.

The request is based on a **Pharmacokinetic (PK) Bridge Study** and a comprehensive **Scientific Justification** regarding the endogenous nature of the active moiety and the predictable release kinetics of the metal-coordinated matrix.

2. SCIENTIFIC JUSTIFICATION

2.1 Endogenous Nature of the Active Moiety

The active pharmaceutical ingredient (API) is Liothyronine (T3), a naturally occurring endogenous hormone. The safety and efficacy profile of Liothyronine is extensively documented in international clinical practice guidelines (e.g., ATA/ETA). As the PZL complex releases chemically identical T3 into the systemic circulation, the biological target and secondary pharmacodynamic effects remain unchanged from the reference product.

2.2 Ligand Exchange Kinetics (Mechanism of Release)

Unlike traditional polymer-based controlled-release systems, which may suffer from erratic "bulk erosion," PZL utilises a **Metal-Ligand Coordination** mechanism.

- The T3 is released via a **zero-order ligand exchange** process governed by the displacement of T3 molecules by water or physiological ions.
- Inorganic characterisation (FTIR/PXRD) confirms a 1:1 molar ratio, ensuring a predictable and reproducible release rate that mimics physiological thyroid secretion.

2.3 Pharmacokinetic Bridging Strategy

The Sponsor has conducted an open-label, randomised PK bridge study (Study PZL-001) comparing the PZL depot to the daily oral reference product.

- **Bioequivalence Criteria:** The total systemic exposure (AUC_{0-t}) of the PZL depot over a 30-day period was found to be within the 80.00% – 125.00% acceptance range relative to the cumulative *AUC* of 30 daily oral doses.

- **Safety Margin:** The suppressed C_{max} of the PZL depot (30% lower than oral) provides an additional safety margin regarding cardiotoxicity.

3. REGULATORY COMPLIANCE (ICH Q3D)

The zinc utilised in the coordination complex (approx. 2.5 mg per dose) is significantly below the **Permitted Daily Exposure (PDE)** for the oral/subcutaneous route as per **ICH Q3D (R2)**. Therefore, the matrix itself introduces no new toxicological concerns.

4. CONCLUSION

The evidence provided demonstrates that Poly-Zinc-Liothyronine is therapeutically equivalent to the reference product while offering a superior safety profile through the avoidance of serum peaks. Based on the **biochemical equivalence** and the **validated PK bridge**, the requirement for additional Phase III clinical trials is considered redundant.