Regulatory & Clinical Documentation Report

Thyme oil and gold ion formulation – preclinical dossier, clinical path and full documentation roadmap

"Built on the foundation of my M.Sc. Biomedical Science research project – where thyme oil showed strong antimicrobial activity and its combination with gold ions displayed strain specific synergy against multidrug-resistant (MDR) Klebsiella pneumoniae – I developed this hypothetical dossier as a forward-looking exercise. The aim is to demonstrate how early laboratory results can be translated into a potential clinical development pathway. By preparing this dossier, I am showcasing my ability to integrate microbiological research findings with regulatory requirements, clinical trial design and international standards (MHRA, EU CTR, ICH GCP and ISO 14155), highlighting both my scientific and medical writing expertise as it would apply in real world drug or device development."

Yash Tarfe
yashtarfee@gmail.com
https://yashtarfe.journoportfolio.com/
14th September, 2025

TABLE OF CONTENTS

Executive summary

My M.Sc. results – thyme oil shows clear antimicrobial and biofilm activity and thyme + gold ions show **strain-dependent synergy** (KP19, KP20) – provide a credible **proof-of-concept** for a **local/topical** therapeutic (wound dressing, topical gel or potentially aerosol for localized respiratory use). For the UK, the **primary regulatory route** for a therapeutic claim will be via MHRA clinical trial authorisation (CTA) leading to potential marketing authorisation (MA) if clinical development succeeds. For device-type applications (e.g. antimicrobial coating on a dressing), EU MDR/UK medical device conformity and ISO 10993 biocompatibility rules would apply. Early scientific advice with MHRA (and EMA HMPC if botanical classification is pursued) is recommended.

1. Product classification and recommended regulatory path

1.1. Medicinal product (if therapeutic claim/wound infection treatment)

- Treat as an investigational medicinal product (IMP) for clinical trials in the UK. Prepare an IMPD as part of a CTA package to MHRA and an ethics submission to a Research Ethics Committee (REC). The MHRA CTA pages describe the application process, required documents and timelines.

1.2. Botanical / Herbal medicinal product considerations

- If it is claimed to have "herbal medicinal" attributes, follow EMA HMPC quality & safety expectations for herbal products (characterisation, standardisation & QC). HMPC guidance is a key reference and will be expected to be included in the dossier, even if we submit primarily to MHRA (European Medicines Agency (EMA), 2024).

1.3. Medical device route (alternative)

- If the intended use is as an antimicrobial coating/dressing (non-systemic), the product may fall under medical device regulations (UK MDR / UKCA or EU MDR if selling in EU) (Medical Device MDCG 2024-5). For devices, ISO 10993 biocompatibility testing and MDCG guidance for device Investigator's Brochure are essential. It is recommended that a parallel evaluation of both paths early (therapeutic vs device) to determine the least onerous route (FDA, 2023).

2. Preclinical (non-clinical) package – what MHRA expects & how my M.Sc. data maps in

- **Documents & content:** IMPD non-clinical section must include clear, traceable data from the M.Sc. experiment and plans for GLP confirmatory studies.

2.1. Pharmacology/Microbiology (what is to be included)

- Raw MIC / MBC tables (CLSI M07 or EUCAST methods), checkerboard FIC matrices and interpretation, biofilm crystal-violet OD tables and time-kill curves (recommended follow-up). Processed QC (ATCC strains) and method SOP citations will be included. This data forms the pharmacology evidence in the **IMPD**.

2.2. In vitro safety testing required before human exposure

- **Cytotoxicity assays** (e.g. MTT or neutral red) on human keratinocytes/epithelial cell lines to estimate selectivity index (SI = IC50 mammalian/MIC bacteria). Report IC50 ± SD and methods. Use this data to justify starting concentrations and dose escalation margins for first-in-human (FIH) trials.

2.3. GLP in vivo studies (to be commissioned)

- **Dermal irritation/sensitisation** (OECD TG 404 / TG 406 alternatives), **repeat-dose dermal toxicity** (28-day dermal in rodent, consider mini pig for human skin surrogate) and **local tolerance**. Include toxicokinetic if systemic exposure is possible. GLP reports go in the IMPD non-clinical section and are required before clinical CTA if systemic exposure is expected. Guidance for nonclinical study expectations for early human trials is summarised in MHRA/EMA/ICH guidance - use MHRA Phase I guidance for FIH dosing strategies (MHRA PHASE 1 ACCREDITATION SCHEME GUIDANCE DOCUMENT, 2025).

2.4. Genotoxicity & other tests

- If systemic exposure is negligible and topical exposure limited, genotoxicity requirements may be assessed; however, typical expectations include at least an Ames test and in vitro micronucleus if systemic exposure is plausible. Any deviation with supportive data should be justified and discussed during pre-submission meeting with MHRA.

2.5. Environmental Risk Assessment (ERA)

- For metal ions (gold), provide an ERA describing persistence and release scenarios from topical use, this will be reviewed by MHRA/UK competent authority as part of the IMPD if environmental exposure is plausible.

3. Chemistry, Manufacturing and Controls (CMC/IMPD)

3.1. Product description & batch documentation

- Provide full composition (active amounts, excipients & vehicle), source, batch CoA for thyme oil (chemotype & thymol/carvacrol content) and gold salt characterization. CoA, Certificates of Analysis for starting materials, raw data for GC-MS (thymol/carvacrol) and ICP-MS (gold) should be appended. MHRA CTA guidance indicates the level of detail expected for IMP manufacture and release (GOV.UK, 2014a).

3.2. Analytical methods & validation

- Analytical assays – validate GC-MS (thymol/carvacrol) for specificity, linearity, accuracy, precision, LOD/LOQ, ICP-MS or AAS for gold quantitation. Provide method validation summaries and sample chromatograms. Release specifications must be declared (assay %, pH, particle size, microbial limits & preservative efficacy). EudraLex/GMP references apply to manufacture of IMP batches (European Commission, 2022).

3.3. Stability plan (ICH Q1A style)

- Describe accelerated and long-term stability protocols and analytical stability-indicating methods. Provide proposed shelf life and storage conditions for clinical batches.

3.4. GMP manufacture & Qualified Person (QP)

- Clinical IMP batches must be manufactured under GMP and QP certified for the clinical trial supply in the UK, MHRA provides guidance and QP requirements in their manufacture FAQs. Document batch records, in-process controls and QP certification for each clinical batch (GOV.UK, 2014b).

4. Safety strategy & FIH dosing (MHRA Phase I expectations)

- Use MHRA Phase 1 accreditation guidance and EMA “First-in-Human” guidance principles to justify starting dose, escalation scheme and stopping rules. Provide cytotoxicity-based safety margins, NOAELs from GLP studies and a proposed

maximal exposure. Include sentinel dosing, cohort escalation rules and clear criteria for halting escalation. MHRA Phase I guidance gives the UK-specific format and expectations for risk mitigation in FIH (MHRA PHASE 1 ACCREDITATION SCHEME GUIDANCE DOCUMENT, 2025).

5. Clinical documentation – protocol, IB, ICF, SAP and RMP

5.1. Investigator's Brochure (IB)

- Non-clinical summary, known human experience (if any), safety monitoring plan, justification for FIH dose and known risks (essential oil irritancy or metal ion exposure). Include references to EMA HMPC for herbal safety discussions (Herbal medicinal products, European Medicines Agency).

5.2. Phase I Protocol (example contents)

- Title, objectives (safety/tolerability primarily), population (healthy volunteers for dermal safety or patients for infected wounds), inclusion/exclusion criteria, dosing schema, safety assessments (dermal scoring, AE/SAE collection, serum gold if relevant) and lab tests. Define stopping criteria and SAE reporting timelines per MHRA rules (GOV.UK, 2014a).

5.3. Informed Consent Form (ICF) & Participant Information Sheet (PIS)

- Clearly state potential risks (irritation, allergy & unknown systemic absorption), monitoring, data protection and withdrawal procedures. Include contact points for AE reporting and Sponsor responsibilities.

5.4. Statistical Analysis Plan (SAP)

- Define primary analyses (safety summaries), exploratory microbiological endpoints (change in log10 CFU), multiplicity control and ITT vs per protocol. Include interim analysis plan (futility/safety only) and DSMB/safety monitoring structure if warranted.

5.5. Risk Management Plan (RMP / PV)

- Dermal sensitization, renal monitoring (if systemic metal absorption plausible), resistance surveillance and environmental monitoring. PV reporting per MHRA timelines (SUSARs & DSUR annually).

6. Medical Device / Biocompatibility considerations (ISO 10993 path) — if device route chosen

- If development pivots to an **antimicrobial device/dressing**, **ISO 10993** series is to be followed for biological evaluation and ISO guidance on sample preparation and testing selection. Provide a biological evaluation plan (BEP) mapping clinical use, contact duration and appropriate ISO tests: cytotoxicity (10993-5), sensitization (10993-10), irritation (10993-10) and systemic toxicity (10993-11) as applicable (FDA, 2023). Use MDCG/ISO guidance for Investigator's Brochure content for device clinical investigations (Medical Device MDCG 2024-5).

7. How my MSc data will be integrated into the MHRA CTA / IMPD

- **Pharmacology evidence:** MIC/MBC/FIC raw tables and biofilm assay results will be presented in IMPD pharmacology section, with methods cited to CLSI/EUCAST.
- **Justification for FIH:** Cytotoxicity SI and proposed GLP dermal data will be used to derive safe starting concentrations and escalation margins referenced to MHRA Phase I guidance.
- **CMC:** CoA for the thyme oil batch used in M.Sc. work (if available), analytical chromatograms and SOPs for your lab methods will be included as annexes illustrating data provenance and traceability.
- **Appendices:** Raw datasets, poster images (labelled as summary) and method SOPs (MIC, checkerboard & crystal violet) will be attached. These show traceability and reproducibility to MHRA reviewers.

REFERENCES –

1. European Medicines Agency (EMA). (2024). *Herbal Medicinal products: Scientific Guidelines | European Medicines Agency (EMA)*. [online] Available at: https://www.ema.europa.eu/en/human-regulatory-overview/research-development/scientific-guidelines/multidisciplinary-guidelines/herbal-medicinal-products-scientific-guidelines.
2. Medical Device MDCG 2024-5 Guidance on Content of the Investigator's Brochure for Clinical Investigations of Medical Devices. (2024). Available at: https://health.ec.europa.eu/document/download/ee7ee8eb-841a-4085-a8dc-af6d55ebf1bd_en?filename=mdcg_2024-5_en.pdf.
3. FDA (2023). *Contains Nonbinding Recommendations Draft -Not for Implementation Select Updates for Biocompatibility of Certain Devices in Contact with Intact Skin Draft Guidance for Industry and Food and Drug Administration Staff DRAFT GUIDANCE*. [online] Available at: https://www.fda.gov/media/142959/download.
4. MHRA PHASE 1 ACCREDITATION SCHEME GUIDANCE DOCUMENT. (2025). Available at: https://assets.publishing.service.gov.uk/media/67f51edeb7e44efc70acc32b/2._MHRA_Phase_I_Accreditation_Scheme_Guidance.pdf.
5. GOV.UK (2014). *Clinical Trials for medicines: Apply for Authorisation in the UK*. [online] GOV.UK. Available at: https://www.gov.uk/guidance/clinical-trials-for-medicines-apply-for-authorisation-in-the-uk.
6. European Commission (2022). *EudraLex - Volume 4*. [online] health.ec.europa.eu. Available at: https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en.
7. GOV.UK (2014b). *Good manufacturing practice and good distribution practice*. [online] GOV.UK. Available at: https://www.gov.uk/guidance/good-manufacturing-practice-and-good-distribution-practice.
8. www.ema.europa.eu. (n.d.). *Herbal medicinal products | European Medicines Agency*. [online] Available at: https://www.ema.europa.eu/en/human-regulatory-overview/herbal-medicinal-products.