USER REQUIREMENTS SPECIFICATION

Hot Melt Extruder

Scope A — Research & Development Scale

Throughput: 1.5 – 3.0 kg/h
Amorphous Solid Dispersions • Formulation Screening • Scale-up Studies

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1. Purpose and Background

This User Requirements Specification (URS) defines the functional, technical, regulatory, safety, and qualification requirements for the procurement of a Hot Melt Extruder (HME) at Research & Development scale (Scope A). The equipment is intended to support pharmaceutical formulation development activities, specifically:

- Amorphous Solid Dispersion (ASD) development for BCS Class II/IV APIs
- Formulation screening with minimal API consumption
- Scale-up studies bridging lab-scale to pilot/production scale

This document shall serve as the binding basis for vendor evaluation, equipment selection, Factory Acceptance Testing (FAT), Site Acceptance Testing (SAT), and subsequent qualification (IQ/OQ/PQ) in accordance with EU GMP Annex 11, 21 CFR Part 11, and ICH Q8/Q9/Q10 guidelines.

2. Scope of Supply

This URS applies to:

- A co-rotating, fully intermeshing twin-screw extruder with throughput range 1.5 to 3.0 kg/h.
- All product-contact subsystems: feeding assembly, barrel/screw assembly, die assembly, and pelletizer or strand cutter.
- Equipment designed for easy manual disassembly and cleaning between product changeovers.
- Advanced process control and data acquisition system (PLC/HMI, OPC UA, 21 CFR Part 11 compliant).
- FAT/SAT execution support and GMP documentation / validation package.
- Downstream processing equipment: the vendor shall include in the proposal a size reduction system, cooling conveyor or belt, calendering unit, and milling system suitable for pharmaceutical ASD extrudate processing. These may be supplied as integrated modules or as validated ancillary equipment from the same vendor.

Exclusions: drying, analytical instruments, and building HVAC/EHS infrastructure are out of scope unless explicitly stated.

3. Applicable Regulations and Standards

Reference	Relevance
EU GMP Annex 11	Computerised Systems – electronic data, audit trails, access control
21 CFR Part 11	Electronic Records & Electronic Signatures (FDA)
21 CFR Part 211	cGMP – equipment design, maintenance, cleaning validation
EU GMP Annex 15	Qualification and Validation lifecycle
ICH Q8(R2)	Pharmaceutical Development – QbD / Design Space
ICH Q9	Quality Risk Management
ICH Q10	Pharmaceutical Quality System
GAMP 5 (2nd Ed.)	Software categorisation for PLC/SCADA; vendor documentation requirements
ISPE Good Practice Guide: HME	Industry guidance for hot melt extrusion in pharmaceutical manufacturing
ISO 14644-1/-2	Cleanroom classification relevant to installation environment

EN ISO 13857 / 2006/42/EC	Machinery safety guarding; CE marking
ATEX 2014/34/EU	As applicable for processing low ignition-point excipients
ISO 11135 / EN 1672-2	Hygienic design and cleanability
EU GMP Part 1 Chapter 3	Premises and Equipment
ISPE Baseline Guide Vol. 5, 2nd Ed.	Commissioning & Qualification
ISPE Baseline Guide Vol. 7, 2nd Ed.	Risk-Based Manufacture of Pharma Products

4. General and Configuration Requirements

Req. ID	Requirement	Type
GEN-001	The equipment shall be a co-rotating, fully intermeshing twin-screw extruder designed and validated for pharmaceutical processing.	M
GEN-002	The nominal screw diameter shall be 11 mm, providing throughput coverage of 1.5 to 3.0 kg/h for typical pharmaceutical polymer/API blends.	M
GEN-003	The equipment shall have a modular screw and barrel design with geometric equivalence to larger production-scale extruders to enable direct scale-up without reformulation.	M
GEN-004	The barrel shall consist of a minimum of 6 independently controlled, individually removable heating/cooling zones.	M
GEN-005	The L/D ratio shall be ≥ 40:1 to ensure adequate residence time for ASD processing.	M
GEN-006	All product-contact surfaces shall be manufactured from pharmaceutical-grade corrosion-resistant materials (316L stainless steel or equivalent high-alloy tool steel). Surface roughness Ra ≤ 0.8 µm.	M
GEN-007	Barrel segments shall be horizontally split (clamshell design) or modular bolted for ease of opening, inspection, screw removal, and manual cleaning without major disassembly.	M
GEN-008	The equipment shall be CE marked and comply with the EU Machinery Directive 2006/42/EC.	M
GEN-009	The vendor shall demonstrate a documented installed base of equivalent equipment in GMP-regulated pharmaceutical facilities.	M
GEN-010	Equipment footprint shall be compatible with a standard pharmaceutical development laboratory (floor-standing, max 2.0 m width × 1.5 m depth).	D

M = Mandatory | D = Desirable | I = Informational

5. Process Parameter Requirements

5.1 Throughput and Operating Range

Parameter	Required Range	Unit	Notes
Throughput – minimum	0.1	kg/h	Scope A lower bound for formulation screening
Throughput – maximum	5.0	kg/h	Hard upper bound for R&D/clinical batch scale
Screw diameter	11	mm	Nominal; vendor to confirm exact bore geometry
Screw speed (minimum)	2	rpm	For heat-sensitive formulations

Screw speed (maximum)	Per vendor spec.	rpm	Vendor to specify maximum rated speed for proposed drive/gearbox
Speed accuracy	± 1	rpm	—
L/D ratio	≥ 40:1	—	Required for ASD processing and adequate mixing
Barrel temp. range	20 – 350	°C	Per zone, independently controlled
Temperature accuracy	± 1	°C	At steady-state per zone
Die pressure (max)	200	bar	For dense polymer matrices
Torque (real-time)	Yes	N·m / %	Overload protection mandatory
Specific energy input	Monitorable	kWh/kg	Critical process parameter for ASD QbD design space

5.2 Feeder System

- At least one gravimetric loss-in-weight (LIW) feeder shall be provided as the primary powder feed stream.
- A second feeder port or side-stuffer port shall be provided for liquid injection or secondary solid addition.
- Feeder screws shall be interchangeable to accommodate a wide bulk density range (0.1 – 1.2 g/mL).
- Feeder gravimetric accuracy: ≤ ± 1.0% of set-point at steady state.
- All feeder product-contact surfaces shall meet the same material and surface finish standards as the extruder barrel.
- Feeder hopper and all product-contact parts shall be easily removable for manual cleaning without special tools.

5.3 Screw Configuration

Screws shall be modular (self-wiping, splined shaft) allowing configuration with conveying, kneading (forward/reverse), and mixing elements. Rapid changeover: complete screw change shall be achievable in ≤ 30 minutes by a single operator using only supplied tooling. Screw elements shall be compatible with scale-up: identical OD/ID ratios and pitch/geometry to the vendor's larger pharma-scale extruder family.

The vendor shall supply a minimum of 2 pre-validated screw configurations optimised for ASD processing, with documented process parameters. The preferred baseline screw functional pattern is defined below. The vendor shall propose element-specific geometry (pitch, disc width, element length) from their product catalogue for the proposed 11 mm screw diameter class to match this functional zone architecture.

5.3.1 Reference Screw Configuration RC-01 — Functional Zone Pattern

11 element positions | L/D ≥ 40:1 | Co-rotating twin screw | Slit die (vendor to dimension)

Pos.	Element Type	Count	Process Zone	Function
1	Coupling / drive entry	1	Drive entry	Shaft coupling element; connects to gearbox spline and initiates material intake into the barrel
2	Shovel conveying	14	Feed / intake zone	High-pitch shovel conveying elements for starve-fed powder intake; prevents fluidisation of light powders
3	Transition (conveying →	1	Transition	Bridges from high-pitch conveying to

	mixing)			tighter-pitch zones; gradually increases degree of fill before first mixing zone
4	Kneading block (45° forward, 5 disc)	1	Mixing zone 1	First kneading block; moderate dispersive shear for initial softening and partial melting of polymer-API blend
5	Standard conveying	9	Melting / conveying	Standard-pitch conveying elements; extended residence time for conductive heat transfer and gradual melting
6	Kneading block (45° forward, 5 disc)	2	Intensive mixing	Two consecutive forward kneading blocks; main dispersive mixing zone for complete API dissolution into molten polymer carrier (ASD formation)
7	Neutral kneading block (90°, 5 disc)	1	Restrictive zone	Neutral stagger kneading block; zero net forward conveying, creates pressure seal and maximum residence time for API-polymer homogeneity; melt seal between mixing and metering zones
8	Standard conveying	1	Pressure relief	Pressure relief element after restrictive zone; prevents excessive melt temperature buildup; optional vent/degassing port location
9	High-pitch metering conveying	4	Metering zone	Increased-pitch metering elements; lower shear, stabilises melt pressure and temperature for uniform volumetric flow to die
10	Shovel conveying	3	Die feeding	Shovel elements for final pressure building toward the die; high conveying efficiency ensures consistent volumetric flow rate
11	Transition (conveying → die)	1	Die entry	Final transition element; smooths melt flow velocity profile for uniform distribution across the die opening

Total element count: 38 individual elements across 11 positional groups.

Zone summary (target proportional distribution):

Process Zone	Share (%)	Element Positions	Primary Function
Feed / intake	~40	1–3	Powder intake and initial conveying (shovel elements)
Mixing zone 1	~2.5	4	Initial softening and partial melting (forward KB)
Melting / conveying	~22.5	5	Extended residence time for conductive heat transfer
Intensive mixing	~5	6	Main dispersive mixing for ASD formation (2× forward KB)
Restrictive zone	~2.5	7	Melt seal / pressure dam (90° neutral KB)
Pressure relief	~2.5	8	Temperature relief; optional vent/degassing port

Metering / die feed	~25	9–11	Melt pressure stabilisation and uniform die flow

Note: Element type descriptions are functional and vendor-agnostic. The vendor shall map each position to their proprietary element catalogue and propose specific element part numbers, pitches, and lengths appropriate for the offered screw diameter. Zone proportions are target values; the vendor may propose minor deviations with documented process justification.

6. Cleaning and Hygienic Design Requirements

The equipment shall be designed for rapid, thorough manual disassembly and cleaning between product changeovers. CIP/WIP capability is not required; however, the design shall prioritise ease of manual cleaning to support cleaning validation.

Req. ID	Requirement	Type
CLN-001	All product-contact parts (barrel segments, screw elements, die assembly, feeders) shall be removable by a single operator for manual cleaning using only the supplied tool kit, without the need for heavy lifting equipment.	M
CLN-002	Complete disassembly for cleaning shall be achievable within 60 minutes by a trained operator.	D
CLN-003	All product-contact surfaces shall have a surface roughness Ra ≤ 0.8 µm (documented measurement certificates required at FAT).	M
CLN-004	Equipment design shall minimise dead legs, threads, crevices, and pooling zones that could harbour API residue or cleaning agents.	M
CLN-005	The barrel bore and all internal product-contact surfaces shall be fully drainable (no pooling zones) when the barrel is opened or disassembled.	M
CLN-006	The vendor shall supply a documented manual cleaning procedure specifying: cleaning agents, concentrations, temperatures, contact times, and recommended swabbing locations for cleaning validation.	M
CLN-007	All lubrication points shall be isolated from the product zone (sealed bearings or equivalent) to prevent lubricant contamination.	M
CLN-008	All seals, O-rings, and gaskets in product-contact zones shall be selected for chemical compatibility with common pharmaceutical solvents and excipients (e.g., EPDM, PTFE, Viton as appropriate) and shall be individually replaceable.	M

7. Heating and Cooling Requirements

Req. ID	Requirement	Type
HC-001	Each barrel zone shall have an independent PID-controlled electrical heater with active forced-air or liquid cooling.	M
HC-002	Zone temperature control accuracy: ± 1°C at steady state.	M
HC-003	The cooling system shall reduce barrel temperature from 200°C to below 80°C within 15 minutes to support rapid product changeover.	D
HC-004	A dedicated cooling/controlled-temperature zone shall be present in the final barrel segment before the die.	M
HC-005	Die temperature shall be independently controlled from barrel zones.	M
HC-006	All temperature sensors shall be Pt100 Class A (IEC 60751) with documented calibration traceability.	M
HC-007	An emergency cooling sequence shall activate automatically upon	M

	temperature exceedance alarm, with HMI alert and audit trail entry.	

8. Process Control and Data Acquisition System

8.1 General Control

Req. ID	Requirement	Type
CS-001	A dedicated PLC-based control system with touch-screen HMI (minimum 12-inch display) shall be supplied.	M
CS-002	All Critical Process Parameters (CPPs) shall be logged at ≥ 1 Hz with ISO 8601 time-stamping; minimum CPPs: screw speed, torque (%), zone temperatures, die temperature, die pressure, feeder rate, specific energy input.	M
CS-003	Recipe management: storage of ≥ 50 named process recipes with version control and change history.	M
CS-004	Configurable alarming per parameter (high/low, deviation) with alarm logging and mandatory acknowledgement records.	M
CS-005	The control software shall be classified per GAMP 5 Category 4 or 5; vendor shall provide the full software documentation package (SDD, SRS, test protocols).	M
CS-006	The system shall expose an OPC UA server (or equivalent IEC 62541-compliant interface) enabling real-time tag subscription and historical data access from SCADA/MES platforms.	M
CS-007	Data export shall be possible in open formats (CSV, JSON, XML) without requiring proprietary licensed software for data retrieval.	M
CS-008	Remote monitoring capability via Ethernet/TCP-IP shall be provided.	D
CS-009	The control system shall support PAT (Process Analytical Technology) instrument integration through a minimum of 2 spare analogue/digital I/O channels or a dedicated PAT communication port.	D

8.2 GMP Data Integrity and 21 CFR Part 11 Compliance

Req. ID	Requirement	Type
GMP-001	A complete, time-stamped, tamper-evident electronic audit trail shall capture all operator actions, recipe activations, parameter overrides, and alarm events.	M
GMP-002	Role-based access control (RBAC) shall enforce minimum 3 user levels: Operator, Supervisor, Administrator. Generic or shared accounts are prohibited.	M
GMP-003	Electronic signatures compliant with 21 CFR Part 11 Subpart C shall be enforced for critical operations (recipe activation, parameter override above defined limits, audit trail review sign-off).	M
GMP-004	Process data shall be stored in a non-editable, non-deletable format; any attempted modification shall be captured in the audit trail.	M
GMP-005	The vendor shall supply a Vendor Assessment Questionnaire (VAQ), Software Description Document (SDD), and a Change Control procedure for the control software covering a minimum 10-year horizon.	M
GMP-006	Backup and recovery procedures shall be documented, executable from the HMI, and validated by the vendor.	M
GMP-007	System clock shall be synchronisable to a facility NTP server for time-stamp traceability.	M

GMP-008	The system shall support integration with MES/SCADA platforms via OPC UA for batch record population; vendor shall provide an OPC UA node map / address space documentation.	M

9. Vacuum Degassing Requirement

- Integrated, modular vacuum degassing capability located within the final barrel sections prior to the die to enable efficient removal of entrapped air, moisture, and volatile components from the molten formulation during processing.
- Independently adjustable and precisely controlled, suitable for continuous GMP operation.
- Fully integrated into the extruder control system, enabling real-time monitoring and control of vacuum parameters via the HMI/PLC interface.

10. Die Assembly and Downstream Processing

10.1 Die Assembly

- Standard strand die (2–4 strands, interchangeable orifice diameter 1–4 mm) shall be supplied.
- A slit die shall be available as a standard or optional configuration, dimensioned for the proposed screw diameter. Vendor to specify die geometry and opening dimensions.
- Die changeover shall be achievable within 15 minutes using standard supplied tooling.
- All die product-contact surfaces: 316L SS, Ra ≤ 0.8 µm.
- Melt pump coupling interface (optional/desirable): provision for melt pump installation to stabilise die pressure independently of screw speed.

10.2 Downstream Processing Equipment

The vendor shall propose and include in the scope of supply the following downstream processing modules, designed for pharmaceutical ASD extrudate handling. All product-contact surfaces shall be 316L SS with Ra ≤ 0.8 µm and shall be easily disassembled for manual cleaning.

Req. ID	Downstream Module	Requirement	Type
DS-001	Cooling system	A cooling conveyor, cooling belt, or equivalent system shall be provided to reduce the extrudate temperature from melt temperature to a handleable state suitable for downstream size reduction. The cooling rate and belt speed (if applicable) shall be adjustable. Temperature monitoring at discharge shall be provided.	M
DS-002	Calendering unit	A calendering (flaking) roll system shall be provided for forming the cooled extrudate into a uniform sheet or flake suitable for milling. Roller gap, speed, and temperature (if heated/cooled rolls) shall be adjustable. Roller surface finish shall meet pharmaceutical product-contact requirements.	M
DS-003	Milling system	A size reduction / milling unit shall be provided for reducing calendered flakes or extrudate strands to a defined particle size distribution suitable for downstream blending and tabletting/encapsulation. Screen size shall be interchangeable. The vendor shall specify achievable particle size range (target d50 and d90).	M
DS-004	Size reduction	Optional pelletizer attachment (hot-face or strand cut) shall	D

	(pelletizer)	be available as a validated accessory, as an alternative to the calendering/milling route.	
DS-005	Integration	All downstream modules shall be mechanically and electrically compatible with the extruder system. Process parameters of downstream equipment (belt speed, roller gap, mill speed) shall be monitorable and, where feasible, controllable from the extruder HMI or logged to the same data acquisition system.	M
DS-006	Cleaning	All downstream product-contact parts shall be removable for manual cleaning without special tools, consistent with the cleanability requirements in Section 6.	M

11. Safety Requirements

Req. ID	Requirement	Type
SAF-001	All rotating parts and heated surfaces shall be guarded per EN ISO 13857 and the EU Machinery Directive 2006/42/EC.	M
SAF-002	Emergency stop (E-stop): accessible to operator at all working positions; activation stops all drives and feeders within 2 seconds with audit trail entry.	M
SAF-003	Torque overload protection shall automatically stop the screw drive on detection of excess torque, with HMI alarm and data log entry.	M
SAF-004	Independent over-temperature safety cut-outs on all heater zones, set at maximum 20°C above process set-point (not software-based only — hardware interlock required).	M
SAF-005	Die pressure relief or burst disc protection rated to maximum operating pressure shall be installed.	M
SAF-006	Barrel vent connection(s) for managing off-gases or fumes shall be provided.	M
SAF-007	ATEX classification documentation shall be provided for all components handling potentially flammable polymer melts or solvents, as applicable.	D
SAF-008	All safety interlocks shall be documented in a Machine Safety Risk Assessment supplied with FAT documentation.	M

12. Utility and Installation Requirements

12.1 Electrical Supply

- Supply voltage: 400 V / 3-phase / 50 Hz. Control and HMI: 230 V / 1-phase / 50 Hz.
- Total connected load: ≤ 20 kVA (target for this scale; vendor to confirm).
- Compliance with EN 60204-1 (Safety of Machinery – Electrical Equipment).

12.2 Cooling

- Forced-air cooling preferred (self-contained, no facility chilled water required).
- If liquid cooling is required, vendor shall specify: min/max inlet temperature, flow rate (L/min), supply pressure, and connection type.

12.3 Compressed Air / Instrument Air

- If pneumatic components are incorporated: 6 bar(g), quality class 1.4.1 per ISO 8573-1.

12.4 Environment

- Operating environment: 15–30°C ambient, 20–65% RH non-condensing.

- Drive/control enclosure protection rating: minimum IP54.

13. Vendor Documentation Package

The vendor shall supply a complete GMP documentation package structured to support the full commissioning, qualification, and validation lifecycle per EU GMP Annex 15 (2015), ISPE Baseline Guide Volume 5, 2nd Edition, and GAMP 5 (2nd Edition). All documentation shall be delivered in English, in both hardcopy and electronic (PDF) format, no later than the agreed FAT date unless otherwise specified.

13.1 Design and Engineering Documentation

Req. ID	Requirement	Type
DOC-001	General Arrangement (GA) drawings showing all major assemblies, product-contact zones, and utility connection points.	M
DOC-002	Piping and Instrumentation Diagrams (P&IDs) for all process, utility, and pneumatic circuits.	M
DOC-003	Electrical schematics including power distribution, control wiring, I/O allocation lists, and motor data sheets.	M
DOC-004	Material certificates (EN 10204 Type 3.1) for all product-contact components, including barrel segments, screw elements, die assembly, and feeder product-contact parts.	M
DOC-005	Surface roughness measurement certificates (Ra ≤ 0.8 µm) for all product-contact surfaces, measured and documented per ISO 4287.	M
DOC-006	Bill of Materials (BOM) for all product-contact components and critical wear parts with manufacturer part numbers.	M
DOC-007	Machine Safety Risk Assessment per 2006/42/EC and EN ISO 12100, supplied at or before FAT.	M
DOC-008	GMP Declaration of Conformity signed by the vendor confirming the equipment is designed, manufactured, and documented for pharmaceutical GMP manufacturing.	M
DOC-009	CE Declaration of Conformity per EU Machinery Directive 2006/42/EC.	M

13.2 Software and Control System Documentation

Req. ID	Requirement	Type
DOC-010	GAMP 5 software documentation package: Software Requirements Specification (SRS), Software Design Specification (SDS/SDD), Software Configuration Specification, and module/unit test records.	M
DOC-011	Software functional risk assessment (GAMP 5 Appendix M4) identifying GMP-critical functions, associated risks, and mitigating controls verified during OQ.	M
DOC-012	OPC UA address space / node map documentation listing all exposed tags, data types, engineering units, and update rates for SCADA/MES integration.	M
DOC-013	User access and role configuration guide, specifying factory-default RBAC settings and instructions for site-specific customisation.	M
DOC-014	Backup, restore, and disaster recovery procedure for all software components, validated by the vendor.	M

13.3 Operations, Maintenance, and Support Documentation

Req. ID	Requirement	Type

DOC-015	Operations Manual covering: start-up/shutdown sequences, normal and abnormal operating procedures, recipe management, and alarm response guidance.	M
DOC-016	Maintenance Manual with preventive maintenance schedule, recommended spare parts list (with lead times and part numbers), lubrication schedule, and troubleshooting guide.	M
DOC-017	Manual cleaning procedure specifying: cleaning agents, concentrations, temperatures, contact times, rinse procedures, and recommended swabbing locations for cleaning validation.	M
DOC-018	Calibration certificates for all supplied instrumentation with traceable national/international standards reference, including as-found/as-left data.	M
DOC-019	Change notification commitment: vendor agrees to notify purchaser ≥ 90 days in advance of any hardware, firmware, or software change that may affect the validated state of the equipment.	M

14. Factory Acceptance Test (FAT) and Site Acceptance Test (SAT)

FAT and SAT form the foundation of the commissioning and qualification lifecycle. They shall be executed per a vendor-prepared, purchaser-approved protocol and shall generate contemporaneous, attributable, legible, original, and accurate records (ALCOA+ principles).

14.1 Factory Acceptance Test (FAT)

Req. ID	Requirement	Type
FAT-001	The vendor shall prepare a written FAT Protocol covering mechanical integrity checks, utility verification, safety device function, control system operation (including HMI screens, alarm logic, recipe management), and a wet/dry test run.	M
FAT-002	FAT shall be executed at the vendor's manufacturing facility; purchaser participation and co-signature of results is mandatory.	M
FAT-003	A punch list / deviation log shall be maintained during FAT execution. All Category A (critical) deviations shall be resolved before shipment; Category B (non-critical) deviations shall be closed before SAT completion.	M
FAT-004	A signed FAT Summary Report documenting all test results, deviations, and agreed corrective actions shall be issued within 10 business days of FAT completion.	M
FAT-005	The FAT shall include a functional demonstration of OPC UA connectivity and data export (CSV/JSON) to verify integration readiness.	M

14.2 Site Acceptance Test (SAT)

Req. ID	Requirement	Type
SAT-001	The vendor shall provide a SAT Protocol verifying correct installation, utility connections, and basic functional operation at the purchaser's site.	M
SAT-002	On-site commissioning support by a qualified vendor field service engineer (minimum 2 days) is included in the scope of supply.	M
SAT-003	The SAT shall confirm resolution of all outstanding FAT punch list items and verify that transport/installation has not introduced damage or deviation from the qualified state.	M
SAT-004	A signed SAT Summary Report shall be issued within 10 business days of SAT completion.	M

15. Installation Qualification (IQ)

The vendor shall supply a fully developed, equipment-specific IQ Protocol with pre-populated acceptance criteria, ready for purchaser review, approval, and execution at the installation site. The IQ shall be structured in accordance with EU GMP Annex 15 (2015) and ISPE Baseline Guide Volume 5, 2nd Edition.

15.1 IQ Protocol Requirements

Req. ID	Requirement	Type
IQ-001	The vendor shall deliver an equipment-specific IQ Protocol (not a generic template) with pre-defined test scripts, acceptance criteria, and data recording forms traceable to this URS and the vendor's design specifications.	M
IQ-002	The IQ Protocol shall include a Requirements Traceability Matrix (RTM) mapping each URS mandatory requirement to its corresponding IQ verification step, test method, and acceptance criterion.	M
IQ-003	The IQ Protocol shall include provision for deviation documentation, impact assessment, and CAPA referencing per the purchaser's site quality system.	M

15.2 IQ Verification Scope

The IQ Protocol shall include, at minimum, verification test scripts for all of the following areas:

Req. ID	IQ Verification Area	Scope / Acceptance Criteria	Type
IQ-010	Equipment identity and as-built verification	Confirm equipment model, serial number, and configuration against purchase order, GA drawings, and P&IDs. Verify nameplate data.	M
IQ-011	Site and location verification	Confirm physical installation location, orientation, access clearances, and environmental conditions meet vendor specifications and site layout drawings.	M
IQ-012	Utility connections	Verify electrical supply (voltage, phase, frequency), compressed air (pressure, quality class), and cooling connections against vendor specifications. Record as-found measurements.	M
IQ-013	Product-contact material certificates	Verify EN 10204 Type 3.1 material certificates for all product-contact components (barrel, screws, die, feeder) against the BOM. Confirm 316L SS or equivalent.	M
IQ-014	Surface finish verification	Verify surface roughness certificates (Ra ≤ 0.8 µm per ISO 4287) for all product-contact surfaces against IQ acceptance criteria.	M
IQ-015	Instrument calibration verification	Verify calibration certificates (as-found/as-left, traceable standards) for all installed instruments: temperature sensors (Pt100), pressure transducers, torque sensors, load cells, speed encoders.	M
IQ-016	Safety device installation	Verify physical installation and wiring of all safety devices: E-stops, guard interlocks, over-temperature cut-outs, torque overload protection, pressure relief/burst discs.	M
IQ-017	Control system and software installation	Verify PLC hardware configuration, HMI software version, firmware versions, and GAMP 5 software category against the Software Configuration Specification. Record installed software revision.	M
IQ-018	Network and	Verify Ethernet/TCP-IP connectivity, OPC UA server	M

	communication	accessibility, and NTP synchronisation configuration.	
IQ-019	Mechanical assembly and lubricant isolation	Verify barrel segment assembly, screw shaft alignment, gearbox coupling, and confirm all lubrication points are isolated from the product zone (sealed bearings).	M
IQ-020	Spare parts and documentation inventory	Verify receipt of all documentation deliverables per Section 13 and all spare parts against the recommended spare parts list.	M

15.3 IQ Summary Report

Req. ID	Requirement	Type
IQ-030	Upon completion, the vendor shall support preparation of an IQ Summary Report documenting: all test results (pass/fail), deviations encountered, CAPA references, and a qualification status statement (Qualified / Qualified with Restrictions / Not Qualified).	M
IQ-031	The IQ Summary Report shall be co-signed by the vendor field service engineer and the purchaser's designated Qualification Lead and QA representative.	M

16. Operational Qualification (OQ)

The vendor shall supply a fully developed, equipment-specific OQ Protocol with pre-populated test scripts and quantitative acceptance criteria, demonstrating that the equipment operates as intended across its specified operating ranges. The OQ shall be structured in accordance with EU GMP Annex 15 (2015) and ISPE Baseline Guide Volume 5, 2nd Edition.

16.1 OQ Protocol Requirements

Req. ID	Requirement	Type
OQ-001	The vendor shall deliver an equipment-specific OQ Protocol (not a generic template) with pre-defined functional test scripts, quantitative acceptance criteria, and data recording forms traceable to this URS and the vendor's Functional Design Specification (FDS).	M
OQ-002	The OQ Protocol shall include a Requirements Traceability Matrix (RTM) mapping each URS mandatory requirement to its corresponding OQ functional test, test method, and acceptance criterion.	M
OQ-003	The OQ Protocol shall include provision for deviation documentation, impact assessment, and CAPA referencing per the purchaser's site quality system.	M
OQ-004	OQ execution shall be performed with vendor field service engineering support on site (minimum 2 additional days beyond SAT).	M

16.2 OQ Functional Test Scope

The OQ Protocol shall include, at minimum, functional test scripts for all of the following areas:

Req. ID	OQ Functional Test Area	Scope / Acceptance Criteria	Type
OQ-010	Screw speed control	Verify screw speed controllability across the full operating range (2 rpm to vendor-rated maximum). Confirm accuracy ± 1 rpm at low (10 rpm), mid (50% of rated max), and high (90% of rated max) set-points. Record steady-state response time.	M
OQ-	Barrel zone	Verify independent PID heating and cooling for each	M

011	temperature control	barrel zone. Challenge at low (60°C), mid (150°C), and high (250°C) set-points. Confirm ± 1°C steady-state accuracy per zone.	
OQ-012	Die temperature control	Verify independent die zone heating. Confirm ± 1°C steady-state accuracy independent of barrel zone settings.	M
OQ-013	Torque monitoring and overload protection	Verify real-time torque display (N·m / %). Trigger torque overload interlock; confirm automatic screw drive stop, HMI alarm, and audit trail entry within 2 seconds.	M
OQ-014	Feeder gravimetric control	Verify loss-in-weight feeder accuracy (≤ ± 1.0% of set-point) at minimum 3 feed rates spanning the operating range. Confirm steady-state and refill transient performance.	M
OQ-015	Die pressure monitoring	Verify die pressure measurement accuracy and response. Confirm pressure alarm activation at configured high-limit and audit trail entry.	M
OQ-016	Emergency stop (E-stop) function	Activate E-stop at each operator station. Confirm all drives and feeders stop within 2 seconds, HMI alarm is generated, and event is recorded in the audit trail.	M
OQ-017	Over-temperature safety interlock	Simulate over-temperature condition (set-point + 20°C) on each barrel zone. Confirm hardware interlock activation (heater de-energised), HMI alarm, and audit trail entry. Verify this is independent of software control.	M
OQ-018	Alarm and event management	Verify configurable alarm set-points (high/low, deviation) for all CPPs. Confirm alarm logging, HMI annunciation, and mandatory operator acknowledgement with audit trail capture.	M
OQ-019	Recipe management	Create, store, recall, and execute a minimum of 3 test recipes. Verify version control, change history logging, and electronic signature enforcement on recipe activation.	M
OQ-020	Data logging and integrity	Verify CPP logging at ≥ 1 Hz with ISO 8601 timestamps. Confirm data is non-editable and non-deletable. Attempt unauthorised data modification and verify rejection with audit trail entry.	M
OQ-021	Audit trail verification	Verify the audit trail captures: operator login/logout, parameter changes, recipe activations, alarm events, and parameter overrides. Confirm entries are time-stamped, attributable (user ID), and tamper-evident.	M
OQ-022	User access control (RBAC)	Verify role-based access for Operator, Supervisor, and Administrator levels. Confirm each role's permissions and restrictions per the access control matrix. Verify generic/shared accounts are blocked.	M
OQ-023	Electronic signatures (21 CFR Part 11)	Verify electronic signature enforcement for critical operations: recipe activation, parameter override beyond defined limits, and audit trail review sign-off. Confirm signature includes user ID, date/time, and meaning.	M
OQ-024	OPC UA communication	Verify OPC UA server connectivity from an external client. Confirm real-time tag subscription for all CPPs, historical data query, and verify tag names/data types match the OPC UA node map documentation.	M
OQ-	Data export	Verify data export in CSV, JSON, and XML formats.	M

025		Confirm exported data completeness and accuracy against logged data for a defined test run.	
OQ-026	NTP time synchronisation	Verify system clock synchronisation to a facility NTP server. Confirm time-stamp accuracy within ± 1 second of reference.	M
OQ-027	Backup and restore	Execute a full system backup. Simulate data loss and perform restore. Verify all recipes, user accounts, configuration, and historical data are recovered without loss or corruption.	M
OQ-028	Emergency cooling sequence	Simulate temperature exceedance alarm. Verify automatic activation of emergency cooling sequence, HMI alert, and audit trail entry.	M
OQ-029	Pressure relief / burst disc	Verify installation and rating of die pressure relief device. Document rated burst pressure and confirm it does not exceed maximum operating pressure.	M
OQ-030	Specific energy input monitoring	Verify real-time calculation and display of specific energy input (kWh/kg). Confirm logged values are consistent with measured torque, speed, and throughput.	D
OQ-031	Vacuum degassing function	Verify vacuum system controllability, real-time monitoring via HMI/PLC, and confirm stable vacuum level during a simulated process run.	M

16.3 OQ Summary Report

Req. ID	Requirement	Type
OQ-040	Upon completion, the vendor shall support preparation of an OQ Summary Report documenting: all functional test results (pass/fail), worst-case challenge data, deviations encountered, CAPA references, and a qualification status statement (Qualified / Qualified with Restrictions / Not Qualified).	M
OQ-041	The OQ Summary Report shall be co-signed by the vendor field service engineer and the purchaser's designated Qualification Lead and QA representative.	M
OQ-042	All raw data (printouts, screenshots, exported data files) generated during OQ execution shall be appended to the OQ Summary Report as controlled attachments.	M

17. Performance Qualification (PQ) Guidance

Performance Qualification is the responsibility of the purchaser and is executed using representative pharmaceutical formulations under conditions simulating routine production. The vendor shall provide the following support:

Req. ID	Requirement	Type
PQ-001	The vendor shall supply a PQ Guidance Document recommending: test formulations (or surrogate compositions), recommended process parameter windows, critical quality attributes (CQAs) to monitor, and suggested acceptance criteria for ASD processing.	M
PQ-002	The vendor shall supply at least 2 pre-validated screw configurations (including one mapping to the reference functional pattern defined in Section 5.3.1) with documented process parameter ranges and expected performance data to serve as PQ starting conditions.	M
PQ-003	Application engineering support for PQ execution: remote consultation during PQ campaign, with on-site support available upon request (quoted separately	D

	if beyond the 12-month application support period).	

18. Qualification Lifecycle and Requalification

Req. ID	Requirement	Type
QL-001	The vendor shall provide a Requirements Traceability Matrix (RTM) mapping every mandatory URS requirement to its corresponding Design Specification (DS), FAT test, IQ verification, and OQ functional test. The RTM shall demonstrate full forward and reverse traceability across the V-model lifecycle.	M
QL-002	The vendor shall define requalification triggers: conditions under which partial or full re-execution of IQ/OQ is required (e.g., major component replacement, firmware/software upgrade, relocation, repair affecting product-contact parts).	M
QL-003	The vendor shall supply a Periodic Review Guidance document recommending the scope and frequency of ongoing qualification review (e.g., annual instrument recalibration, software patch qualification, preventive maintenance verification).	D
QL-004	Change notification commitment: the vendor agrees to notify the purchaser ≥ 90 days in advance of any hardware, firmware, or software change that may affect the validated state of the equipment, and to provide an impact assessment with the notification.	M

19. Training and After-Sales Support

- On-site installation and commissioning support: minimum 2 days by a qualified field service engineer.
- Operator training (minimum 1 day) and maintenance/advanced process training (minimum 1 day) included in scope.
- Application engineering support for ASD formulation development: remote and on-site support available during first 12 months of operation.
- Warranty: minimum 24 months on parts and labour from SAT completion.
- Spare parts and technical support availability: guaranteed minimum 10 years from delivery.
- Service response time: remote diagnosis within 4 business hours; on-site response within 48 hours (Europe).

20. Project Support

The equipment shall be suitable for the following key projects, which define the primary intended use and shall be considered in the mechanical and process design:

- Venetoclax 10 mg, 50 mg and 100 mg film-coated tablets
- Olaparib 100 mg and 150 mg film-coated tablets
- Apalutamide 60 mg and 240 mg film-coated tablets
- Encorafenib 50 mg and 75 mg hard capsules

21. Vendor Evaluation Criteria

Mandatory pre-qualification conditions (knock-out criteria):

- Demonstrated installation references in pharmaceutical GMP environments.
- GAMP 5 compliant control software documentation package available.
- OPC UA interface supported (native or via gateway).
- Equipment-specific IQ and OQ protocols (not generic templates) available for the proposed configuration.

Evaluation Criterion	Weight (%)	Max Score

Technical compliance – mandatory requirements	25	25
IQ/OQ qualification package completeness and quality	20	20
GMP & 21 CFR Part 11 documentation completeness	15	15
Control system – OPC UA, data integrity, SCADA integration	15	15
Cleaning design and cleaning validation support	10	10
Pharmaceutical installed base and references	10	10
Total cost of ownership (CapEx + service + parts)	5	5
TOTAL	**100**	**100**

22. Equipment Scale Assessment Note

The following assessment is based on published vendor specifications and is provided for informational purposes to support equipment selection. It does not constitute an endorsement of any manufacturer.

Based on the Scope A throughput requirement of 1.5 – 3.0 kg/h and the reference screw functional pattern defined in Section 5.3.1, the following equipment scale assessment applies:

Model Scale	Screw Ø (mm)	Throughput Range	Scope A Fit	Notes
Nano scale	5–8	< 0.5 kg/h	NOT SUITABLE	Throughput ceiling well below 1.5 kg/h lower bound
Micro / R&D (TARGET)	11	0.1 – 3.0 kg/h	BEST FIT	Matches target screw diameter; optimal for formulation screening with minimal API consumption
Lab scale	16–18	0.5 – 7.0 kg/h	OVERSIZED	Covers throughput range but oversized for R&D API economy at Scope A volumes
Pilot scale	24–27	2.0 – ~20 kg/h	NOT SUITABLE	Significantly oversized; excessive API consumption for formulation screening

Conclusion: for Scope A, vendors shall propose a system based on an 11 mm screw diameter class. The reference screw functional pattern in Section 5.3.1 defines the required zone architecture; the vendor shall map this to their proprietary element catalogue for the proposed screw diameter. Proposals based on screw diameters below 8 mm or above 16 mm do not meet the Scope A requirements and will be disqualified at technical evaluation.

23. Revision History

Rev.	Date	Author	Description
01	_____	_____	Initial release – general R&D HME requirements
02	_____	_____	Scope A defined: throughput 1.5–3.0 kg/h; HPAPI OEB 5 section added; CIP/WIP, contained feeder refill, OPC UA, and equipment scale assessment incorporated
03	_____	_____	Rev 03: HPAPI/OEB 5 containment requirements removed; CIP/WIP section replaced with manual cleaning

			design requirements; vendor-agnostic reference screw functional pattern (RC-01, 11 element positions) added in Section 5.3.1; screw diameter set to 11 mm; max RPM set to vendor specification; downstream processing (cooling, calendering, milling) added to scope of supply (Section 10.2); fully developed equipment-specific IQ/OQ protocols with pre-populated acceptance criteria, functional test scripts, and RTM traceability added; FAT/SAT, PQ guidance, and qualification lifecycle sections added; all vendor-specific nomenclature removed for supplier neutrality

24. Approval Signatures

Role	Name (Print)	Date	Signature
Prepared By – Process Engineering			
Reviewed By – R&D Manager			
Reviewed By – Quality Assurance			
Approved By – Head of R&D / Site Director			

End of Document – URS-HME-RD-001 Rev. 03