

Approved by: Juris Bundulis
JSC Olpha Chairman of the Board
Olaine, 13. maijs. 2025

Approved by: Ēriks Ivanovskis
JSC Olpha Scientific Office Director
Olaine, 13. maijs. 2025



Technical specification for the tender:

API production technology development and technology transfer (ID No. 2025/05/6)

1. General information about the study sponsor:

Company name: JSC Olpha

Registration No.: 40003007246

Address: Rūpnīcu iela 5, Olaine LV-2114, Latvia

Contact persons:

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2. Technical specification of the procurement object: API production technology development and technology transfer.

Job assignment	<i>API production technology development and technology transfer</i>
Expected deadline for the execution of the Tasks 1 to 7.	Q2 2027.
Task 1. Development of Technology for API	• Technology development report (in accordance with ICH Q7, Q8(R2) and Q11 guideline requirement; where possible, using QbD principles by DoE approach to optimize yields and raw material consumption norms, to improve quality for each step of the process, to develop robust process, and to define Critical Quality Attributes and Critical Process Parameters). • Development of technology for API with patent freedom to operate from the dates defined by the sponsor. • Feasibility Study: - Route of Synthesis scouting; - Small scale development of API synthesis; - Establishment of in process controls; - Gap analyses before Optimization; • Optimization of lab scale manufacturing process. • Optimization of used quality control methods, determine the main sources of material loss (such as removal with mother liquors, decomposition or the formation of byproducts during synthesis). • The report should include the decision on selection and justification of selection of critical regulatory starting materials (RSMs) in accordance with ICH Q11 (and Q&A) principles and quality requirements, as well justification of selection of other raw materials, their suppliers/manufacturers and quality requirements. • The report should include the results of process robustness and reproducibility studies at lab. scale.
Task 2. Manufacturing process scale-up and validation	• Technology scale-up report (in accordance with ICH Q11 guideline requirement; where possible, using QbD principles by DoE approach to optimize yields and raw material consumption norms, to improve quality for each step of the process, to develop robust process, and to define Critical Quality Attributes and Critical Process Parameters). The report should include the decision on selection and justification of selection of critical regulatory starting materials (RSMs) in accordance with ICH Q11 (and Q&A) principles and quality requirements, as well justification of selection of other raw materials, their suppliers/manufacturers and quality requirements. The report should include the results of process robustness and reproducibility studies from lab. scale to kilo scale. Scale-up batch size should not exceed 10 kg.

	• Raw material consumption norms and costs; list of suppliers/manufacturers of raw materials with corresponding CoAs, best bulk prices and proofs of prices (e.g., official offers and/or e-mails from suppliers); calculations of raw materials costs per 1 kg of the API and each isolated intermediate. • Detailed description of kilo-lab synthetic route procedure / protocol including: - Raw materials loadings; - Working process parameters (NOR, PAR); - Critical process parameters with justifications; - In-process control (control points and parameters) with description of corresponding analytical methods and limits; - Recovery of materials (like solvents), if applicable; - Material balance of the process, material flows description; description of the main sources of material loss (such as removal with mother liquors, decomposition, or the formation of by-products during synthesis). - Description of waste handling and disposal for each stage of the process; - Quantitative composition of waste from API synthesis and purification (for each stage of the process); - Reprocessing procedures of API and/or intermediates. - Description of critical crystallization process parameters, as well as critical crystallization scale-up parameters. - Description of handling and disposal of highly hazardous substances (highly toxic, pyrophoric, sensitive to air or water, explosive, etc.). - Process safety study report (reaction calorimetry, DSC, TGA, etc.). - Report on API polymorphism robustness depending on variability of process parameters at the final preparation stage, and on stability of the final product. - MSDS for all substances used. - Description of the manufacturing equipment cleaning procedures for each stage of the technological process (between production operations, and after finalization of production) with justified limits of detection of residuals. - Description and justification of storage conditions, packaging and proposed retest period for isolated intermediates (e.g. based on stability studies). - Providing to the Sponsor the samples of the API (50-200 g), intermediates (20-50 g) and critical raw materials (100-200 g) obtained and/or used at kilo-lab, as well as samples of other raw materials from best price suppliers (the list of raw material samples is to be agreed with the Sponsor). - Technology validation protocol and report (in accordance with ICH Q7, Q8 and Q11 guideline requirement; where possible, using QbD principles by DoE approach to optimize yields and raw material consumption norms, to improve quality for each step of the process, to develop robust process, and to define Critical Quality Attributes and Critical Process Parameters). Validation batch size – 40 kgs. • The produced kilo-lab API batches are provided to the Sponsor.
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Task 3. API characterization and stability	• Report on characterization data for kilo-lab batches of the API (NMR ¹H and ¹³C, MS and IR spectra with signal assignments, UV spectra, XRPD, elemental analysis, TGA/DSC, bulk density, flowability, microscopy and morphology of crystals, hygroscopicity, thermodynamic solubility at different physiological pH, logP / logD, pKa, BSC classification). • Stability study report for kilo-lab batches according to general principles of ICH Q1 and local Pharmacopoeia (Ph.Eur., USP) requirements (long-term, intermediate, accelerated) for min 6 months, including proposed storage conditions and packaging with corresponding justification.
Task 4. Analytical method development and validation	• Description of developed analytical methods for API (incl. XRPD, PSD), intermediates, raw materials, recovered materials and in-process control, equipment cleaning, as well as methods for elemental impurity testing in the API and those for investigation of possible impurities carry-over (non-mutagenic and mutagenic or potentially mutagenic, N-nitrosamines). When developing methods, ICH Q14 guideline should be taken into account. • Validation protocols and reports as a result of validation in the quality system requirements for all developed analytical methods for API (incl. XRPD, PSD), intermediates, regulatory starting materials, equipment cleaning, using principles of ICH Q2 guideline. The appropriate validation reports should be accompanied with validation protocols and corresponding raw data (chromatograms; titrator, balance and other equipment printouts where possible), as well as result calculations and evaluation to ensure a necessary level of data traceability and data integrity as required by GMP. • Report on API forced-degradation and stress-testing studies (in the quality system, and according to guidelines requirements). • Documentation on necessary in-house reference standards of impurities, intermediates and API, including their specifications and methods of analysis; and information about commercially available and used non-pharmaceutical standards and/or samples (vendor, CoA, characterization data). • Results and CoA of testing samples of API, intermediates, raw materials, recovered materials and in-process control by validated analytical methods from lab. scale and kilo-lab studies.
Task 5. Specification package	• Package should include justified Specifications for the API, intermediates, raw materials (incl. reagents, solvents, catalysts), recovered materials and other relevant materials used for manufacturing process, as well as should include justifications for all specifications taking into account ICH guidelines requirements. • Specification for API should be in compliance with requirements of guidelines ICH Q6A, Q3A, Q3C, Q3D, M7, as well as in compliance with general requirements of Ph.Eur. and US Pharmacopoeias, and should include control of at least the following quality attributes: - Appearance / Description; - Identity (min. two different instrumental methods (e.g. IR and UV), plus polymorphic identity by XRPD); - Polymorphic impurity content by XRPD, with justified limit (not necessary if pure form is steadily produced and other forms are not detected, and there is a rationale for this and a report); - Assay (HPLC);

	- Related substances content (known, unknown and total including degradation impurities with limits defined in accordance with ICH Q3A guideline); - Residual solvents content (with limits in accordance with ICH Q3C guideline); - Potential genotoxic/mutagenic/N-nitrosamine impurities content (depending on results of genotoxic/mutagenic/N-nitrosamine impurities risk assessments and carry-over (fate & purge) study results, and with limits in accordance with ICH M7 guideline and recommendations for N-nitrosamines from EMA and FDA); - Elemental impurity/ies content (depending on results of elemental impurities risk assessments and carry-over, and with limits in accordance with ICH Q3D guideline); - Loss on drying and/or Water content (with justified limits); - Solubility; - Clarity of solution; - Sulphated ash / Residue on ignition (NMT 0.10 %); - Particle size distribution, by laser light diffraction; - Microbiological quality (limits for non-sterile APIs); - Other critical quality attributes if relevant (e.g., residual anions content, bulk density tapped and untapped, flowability, crystal morphology); - Definition of storage conditions and packaging, as well as retest date based on stability and forced-degradation study results. • Specifications for critical regulatory starting materials (RSMs) should be in compliance with requirements of ICH Q11 guideline, as well as in compliance with general requirements of Ph.Eur. and US Pharmacopoeias for test methods, and should include control of at least the following quality attributes: - Appearance / Description; - Identity (min. two different instrumental methods (e.g. IR and UV)); - Assay (with justified limits); - Related substances content (known, unknown and total with justified limits as a results of impurities carry-over studies); - Residual solvents content (if relevant, and with justified limits as a results of impurities carry-over studies); - Potential genotoxic/mutagenic/N-nitrosamine impurities content (if relevant, and with justified limits as a results of impurities carry-over studies according to ICH M7 and EMA/FDA guidances on N-nitrosamines); - Elemental impurity/ies content (if relevant, and with justified limits as a results of risk assessment according to ICH Q3D); - Loss on drying and/or Water content (with justified limits); - Sulphated ash / Residue on ignition (with justified limits); - Other critical quality attributes if relevant (e.g., cation content, anion content, pH of solution, etc.); - Definition of storage conditions and packaging, as well as retest date based on stability studies results.
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In addition to the <u>proposed and justified specification</u>, a technical package from the manufacturer/supplier must be provided for each purchased RSM (produced by third party), which must necessarily include a chemical scheme of Route of Synthesis, Specifications, Analysis methods, Stability Studies, a Brief Description of the manufacturing process and its block diagram, a list of all used starting and auxiliary materials, reagents, solvents, catalysts; discussion and characterization on impurities and their carry-over to RSM and control in RSM (organic impurities, inorganic and elemental impurities, residual solvents, mutagenic impurities, N-nitrosamines), as well as additional certificates for the site (for example, GMP) and confirmations of GMP audits from European, American or local agencies, if any. • <u>Specifications for isolated intermediates</u> should be in compliance with requirements of ICH Q11 guideline, as well as in compliance with general requirements of Ph.Eur. and US Pharmacopoeias for test methods, and should include control of at least the following quality attributes: - Appearance / Description; - Identity (min. two different instrumental methods (e.g. IR and UV)); - Assay (with justified limits); - Related substances content (known, unknown and total with justified limits as a results of impurities carry-over studies); - Loss on drying and/or Water content (with justified limits); - Optional: other critical quality attributes if relevant (e.g., residual solvents content, potential genotoxic/mutagenic/N-nitrosamine impurities content, cation content, elemental impurity/ies content, anion content, pH of solution, etc.); - Definition of storage conditions and packaging, as well as retest date based on stability studies results. • <u>Specifications for organic reagents, non-critical raw materials, solvents</u> should be in compliance with requirements of ICH Q11 guideline, as well as in compliance with general requirements of Ph.Eur. and US Pharmacopoeias for test methods, and should include control of at least the following quality attributes: - Appearance / Description; - Identity; - Assay (with justified limits) or Chromatographic purity; - Related substances content (known, unknown and total with justified limits as a results of impurities carry-over studies); - Loss on drying and/or Water content (if relevant, with justified limits); - Other critical quality attributes if relevant; - Definition of storage conditions and packaging, as well as retest date based on specifications or information from suppliers/manufacturers. • <u>Specifications for inorganic reagents and catalysts</u> should be in compliance with requirements of ICH Q11 guideline, as well as in compliance with general requirements of Ph.Eur. and US Pharmacopoeias for test methods, and should include control of at least the following quality attributes: - Appearance / Description;	
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	- Identity; - Assay (with justified limits); - Critical quality attributes showing catalyst activity (for catalysts); - Other critical quality attributes if relevant; - Definition of storage conditions and packaging, as well as retest date based on specifications or information from suppliers/manufacturers. • <u>Specifications for recovered materials</u> (e.g. recovered solvents, intermediates or crude API) must match the specifications for these materials from the main production process (e.g. specification for recovered solvent has to be the same as for commercial fresh solvent). If the quality of the recovered material does not correspond to the quality specification of this material from the main process, then a written justification for the use of such recovered material should be provided in terms of the consistency of the quality of the final product, carry-over of impurities, production process robustness and its reproducibility, as well as the safety of the production process. The specification of the recovered material must be accompanied by the results of analysis and CoAs obtained during the development of the technology and production of the kilo-lab batches. • <u>Quality specifications of commercial raw materials</u> created in accordance with the requirements of this technical specification (included in the package and proposed for technology transfer) have to be confirmed by suppliers/manufacturers and used by them for quality control and release of corresponding raw materials. Statements from suppliers/manufacturers have to be provided that supplier/manufacture use corresponding specification and test methods for quality control and release of the raw material, and for issuing CoAs.
Task 6. Impurity characterization package	• Report on characterization data of known related substances in the API (including nature and source of impurity, actual content of the impurities in the API, proposed and justified limits according to ICH Q3A, chemical scheme of formation and classification of impurities (process-related, degradation, etc.), identification data by NMR ¹H and ¹³C, MS and IR spectra with signal assignments, UV spectra, other relevant identification techniques). • Report on carry-over of impurities study including: - Description and results of spiking experiments for justifying the quality specification limits for intermediates and raw materials, and for in-process control; - Calculation of purge factors (theoretical and/or experimental) and conclusion about fate and purge of possible impurities including organic, genotoxic / mutagenic impurities, N-nitrosamines, residual solvents, etc. • Risk assessment of elemental impurities for kilo-lab batches of the API according to ICH Q3D principles. • Risk assessment of N-nitrosamine impurities for kilo-lab batches of the API according to EMA guidance and recommendations. • Risk assessment of genotoxic / mutagenic impurities for kilo-lab batches of the API according to ICH M7 principles and EMA guidance and recommendations (based on <i>in silico</i>, databases and literature data, results of Ames tests).

	• Samples of standards of known specified impurities in the API, intermediates, raw materials (including potentially mutagenic impurities) with CoA and characterization data. Contacts of suppliers of these impurities samples/standards, or synthetic procedures for in-house synthesis of these impurities with corresponding qualification data. • Report on toxicological qualification of related substances and organic impurities if the proposed production technology does not allow obtaining API with an impurity content below the qualification limits according to ICH Q3A guideline requirements.
Task 7. Technology Transfer (TT) of API	• Before the start of the TT Applicant must provide detailed requirements of equipment: - Provide specifications for any new or modified equipment required for the synthesis route. This should include reactor types, filtration systems, drying units, etc. - Detail requirements for control systems, including automation, monitoring, and data logging systems necessary to control and optimize the process. - Detail the requirements for the receiving facility. - Negotiate on equipment taking into account the technological capabilities and equipment of the Sponsor. • Before the start of the TT, ensure the supply of the selected Key Intermediate produced under the GMP in the quantities required for the TT, and also provide information on manufacturers/suppliers of other necessary raw materials for TT for a timely order. Batch size for TT – approx. 10 kg. • Before start of TT, ensure the supply of required reference standards, impurity standards and consumables for Quality control of manufacturing process and final API. • Protocols for the transfer of developed and validated analytical methods from Applicant to the Sponsor's QC (by comparative testing (AMT) or co-validation techniques). Applicant must define the performance metrics (acceptance criteria) to evaluate the success of the Analytical Method Transfer, including method repeatability, variance and other parameters critical for successful method employment. • Support on reproducibility studies for synthetic process at Sponsor's R&D laboratory (irreproducibility means that the Tasks and/or subtasks of this Technical Specification regarding the synthesis process are not fulfilled by the applicant). • Collection of analytical and process data for pilot batches. Report about pilot production. Update of technology description and manufacturing protocols (if necessary). Optimization of crystallization to obtain pure polymorphic form of API with defined PSD (if necessary). • Technology Transfer should: - Define the performance metrics to evaluate the success of the technology transfer, including batch consistency, yield, purity, and compliance with regulatory requirements. - Clearly outline the acceptance criteria for process validation, scale-up batches, and final product quality; - Provide Technology Transfer protocol; - Review and correct production protocols / batch records for TT at sponsor's site; - Provide on-site support in the process of TT to adapt the production process to the sponsor's production equipment

	- Assessment of reproducibility when transferring technology (both synthesis and analytics), assistance in solving problems. If the transferred technology is not reproduced at Sponsor's site for reasons related to insufficiently developed technology, then the necessary technology updates and improvements is carried out at the expense of the developer. • Define the payment structure based on milestones, with payment due upon successful completion of each phase. • Documentation of Key Intermediate: - Ensure that specifications for intermediate/-s are well-defined, including purity, identity, and content. These specifications should be derived from validated analytical methods and in compliance with pharmacopoeia standards or internal specifications as well as in line with ICH and GMP requirements. - Document the required specifications and control methods for all starting materials used in the manufacture of the API, including intermediates, excipients, and raw materials. - Documentation must outline the QC testing requirements for all raw materials and intermediates, including any in-process controls. - Documentation on QC testing of intermediate/-s and raw materials including Analytical Methods, validations, Quality Specifications. - Risk Assessment Reports of intermediate and starting materials for – N-nitrosamine presence, genotoxic impurities according to ICH M7 and elemental impurities according to ICH Q3D. - Provide Certificate of Analyses of intermediate and starting materials (3 batches). - Documentation of the storage conditions (temperature, humidity, etc.) required for intermediates to maintain their quality and stability. - Readiness to undergo GMP audits as the site for the production of the first stages of the API. • Commercial price offer (should be provided within this offer): - Price should be expressed in EUR/ kg (or USD/ kg); - Price should be given at least for two levels (50 kg, 100 kg) and optimal amount; • Lead time (should be provided within this offer): - Lead time should be expressed in weeks; - Incoterm should be clearly indicated;
Task 8. Key Intermediate commercial supply	Deliverables: - Supply conditions and clearly defined pricing of Key Intermediate for API synthesis. Supporting documentation for Key Intermediate for API dossier (e.g. documentary package in a form of secondary ASMF including all information necessary for creation of Applicant Part and Restricted Part of API dossier)

Other requirements	The Applicant performing the task must follow the methods and quality requirements defined by the study sponsor. It is required that: - The synthesis of API must not rely on the use of temperatures below -5°C for the TT stages from Key Intermediate to the API; - All starting materials, reagents and materials used for TT must be commercially available; - The use of ICH Class 1 solvents is prohibited (benzene, carbon tetrachloride, 1,2-dichloroethane, 1,1-dichloroethene, 1,1,1-trichloroethane). The use of ICH Class 2 solvents and especially chlorinated solvents have to be avoided. - Avoid the use of highly toxic or explosive compounds for TT stages. - Avoid the use of compounds hazardous to the environment (e.g., chloro-containing solvents) for TT stages. - No preparative column chromatography should be used in the main process for the synthesis/purification of the API and intermediates for TT stages. - Minimize the use of highly corrosive reagents (e.g., elemental bromine, fluorides in acidic medium). Also avoid workup procedures that may leave difficult to remove solid residues inside the equipment (e.g., silicic acid or titanium dioxide residues). - Avoid the need for exotic or purpose-built equipment in commercial scale production (electrolysis, photochemistry, deep vacuum distillation, large-scale cooling below -10°C, uniquely shaped agitators), as well as enzymatic reactions and flow reactors for TT stages. Use of such an equipment should be agreed with the Sponsor. - Atom economy and mass efficiency: minimize the combined mass of reagents, solvents, auxiliary materials per kilogram of the product. - The volume efficiency has to be optimized, as high dilutions lead to low productivity. - Preferable number of production stages from commercially supplied intermediates is 2-3, not counting crystallization and solvent recovery stages. Detailed description of pharmaceutically acceptable methods and quality requirements is available from the study sponsor upon e-mail request to the contact persons indicated above. All reports must be submitted electronically, in the form of MS Office documents written in English, as well as signed pdf-files.
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3. Requirements to the Applicant:

1.	The legal status of the Applicant	The Applicant must be an organization engaged in chemical or pharmaceutical research.
2.	Track record of the Applicant	Not less than 3 (three) years experience in the development of synthetic methods suitable for large scale use in the pharmaceutical industry.
3.	The resources of the Applicant	1. The Applicant has sufficient research staff of suitable qualifications in the field of chemistry. 2. The Applicant must have at its disposal the necessary equipment for performing the work described in this Technical Specification (e.g. laboratory jacketed reactors equipped with adjustable thermostats).
4.	Validity term of offer	Until at least 30.06.2025.
5.	Deadline for performing the work	The expected deadline for performing the work is not later than Q2, 2027 . The deadline may be extended if additional and justified research becomes necessary (justification should be officially provided). The detailed conditions will be specified in Contract.
6.	Scope of work	The Applicant is expected to make an Offer covering the full scope of the Procurement Object.
8.	Equivalent offers	In case if an equivalent is possible to the requirements listed in this Technical Specification, which has not been anticipated by the Study Sponsor, the Applicant may submit an offer meeting the equivalent requirements.
9.	Offer price	The overall contract price and the price for each item listed in the "Work to be performed" section must be indicated in EUR (without VAT). The offer must contain separated information on the cost of purchasing additional raw materials, if not included in the total cost of Tasks. All Costs in offer must contain fixed price for each items in offer (Tasks, Raw materials and other costs) and overall price for all offer.
10.	Payment schedule	The Applicant agrees that the payment schedule and conditions will be defined in the Contract.
11.	Requirements for the formatting of Offer	- The Offer must be submitted in 1 copy prepared in digital format in English; - The date and place of the document preparation must be indicated, along with the name and signature of the responsible person, the legal address and registration number of the Applicant; The Offer must be mailed or delivered to the following address: Mārtiņš Kopeika, Project Manager, phone +371 27207950, Martins.Kopeika@olpha.eu Kristīne Krūmiņa, Project Manager, phone +371 27201531, Kristine.Krumina@olpha.eu

4. Documents to be submitted:
Description of the work to be performed in accordance with the Technical Specification of the Procurement Object (Technical and Financial Offer – Annex No.1).

5. Additional conditions
This procurement is organized within the framework of Project No. 1.2.1.2.i.2/1/24/A/CFLA/005.

6. Annexes:
1. Technical and financial offer.

Technical and financial offer

Item	Work to be performed	Offer from the Applicant	Price without VAT (EUR)	Time required, weeks
1.	Task 1. Development of Technology for API. • Technology development report (in accordance with ICH Q7, Q8(R2) and Q11 guideline requirement; where possible, using QbD principles by DoE approach to optimize yields and raw material consumption norms, to improve quality for each step of the process, to develop robust process, and to define Critical Quality Attributes and Critical Process Parameters). • Development of technology for API with patent freedom to operate from the dates defined by the sponsor. • Feasibility Study: - Route of Synthesis scouting; - Small scale development of API synthesis; - Establishment of in process controls; - Gap analyses before Optimization; • Optimization of lab scale manufacturing process. • Optimization of used quality control methods, determine the main sources of material loss (such as removal with mother liquors, decomposition or the formation of byproducts during synthesis). • The report should include the decision on selection and justification of selection of critical regulatory starting materials (RSMs) in accordance with ICH Q11 (and Q&A) principles and quality requirements, as well justification of selection of other raw materials, their suppliers/manufacturers and quality requirements. • The report should include the results of process robustness and reproducibility studies at lab. scale.			
2.	Task 2. Manufacturing process scale-up and validation • Technology scale-up report (in accordance with ICH Q11 guideline requirement; where possible, using QbD principles by DoE approach to optimize yields and raw material consumption norms, to improve quality for each step of the process, to			

	develop robust process, and to define Critical Quality Attributes and Critical Process Parameters). The report should include the decision on selection and justification of selection of critical regulatory starting materials (RSMs) in accordance with ICH Q11 (and Q&A) principles and quality requirements, as well as justification of selection of other raw materials, their suppliers/manufacturers and quality requirements. The report should include the results of process robustness and reproducibility studies from lab. scale to kilo scale. Scale-up batch size should not exceed 10 kg. • Raw material consumption norms and costs; list of suppliers/manufacturers of raw materials with corresponding CoAs, best bulk prices and proofs of prices (e.g., official offers and/or e-mails from suppliers); calculations of raw materials costs per 1 kg of the API and each isolated intermediate. • Detailed description of kilo-lab synthetic route procedure / protocol including: - Raw materials loadings; - Working process parameters (NOR, PAR); - Critical process parameters with justifications; - In-process control (control points and parameters) with description of corresponding analytical methods and limits; - Recovery of materials (like solvents), if applicable; - Material balance of the process, material flows description; description of the main sources of material loss (such as removal with mother liquors, decomposition, or the formation of by-products during synthesis). - Description of waste handling and disposal for each stage of the process; - Quantitative composition of waste from API synthesis and purification (for each stage of the process); - Reprocessing procedures of API and/or intermediates. - Description of critical crystallization process parameters, as well as critical crystallization scale-up parameters. - Description of handling and disposal of highly hazardous substances (highly toxic, pyrophoric, sensitive to air or water, explosive, etc.). - Process safety study report (reaction calorimetry, DSC, TGA, etc.).		
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	- Report on API polymorphism robustness depending on variability of process parameters at the final preparation stage, and on stability of the final product. - MSDS for all substances used. - Description of the manufacturing equipment cleaning procedures for each stage of the technological process (between production operations, and after finalization of production) with justified limits of detection of residuals. - Description and justification of storage conditions, packaging and proposed retest period for isolated intermediates (e.g. based on stability studies). - Providing to the Sponsor the samples of the API (50-200 g), intermediates (20-50 g) and critical raw materials (100-200 g) obtained and/or used at kilo-lab, as well as samples of other raw materials from best price suppliers (the list of raw material samples is to be agreed with the Sponsor). - Technology validation protocol and report (in accordance with ICH Q7, Q8 and Q11 guideline requirement; where possible, using QbD principles by DoE approach to optimize yields and raw material consumption norms, to improve quality for each step of the process, to develop robust process, and to define Critical Quality Attributes and Critical Process Parameters). Validation batch size – 40 kgs. • The produced kilo-lab API batches are provided to the Sponsor.		
3.	Task 3. API characterization and stability • Report on characterization data for kilo-lab batches of the API (NMR ¹H and ¹³C, MS and IR spectra with signal assignments, UV spectra, XRPD, elemental analysis, TGA/DSC, bulk density, flowability, microscopy and morphology of crystals, hygroscopicity, thermodynamic solubility at different physiological pH, logP / logD, pKa, BSC classification). • Stability study report for kilo-lab batches according to general principles of ICH Q1 and local Pharmacopoeia (Ph.Eur., USP) requirements (long-term, intermediate, accelerated) for min 6 months, including proposed storage conditions and packaging with corresponding justification.		
4.	Task 4. Analytical method development and validation		

	• Description of developed analytical methods for API (incl. XRPD, PSD), intermediates, raw materials, recovered materials and in-process control, equipment cleaning, as well as methods for elemental impurity testing in the API and those for investigation of possible impurities carry-over (non-mutagenic and mutagenic or potentially mutagenic, N-nitrosamines). When developing methods, ICH Q14 guideline should be taken into account. • Validation protocols and reports as a result of validation in the quality system requirements for all developed analytical methods for API (incl. XRPD, PSD), intermediates, regulatory starting materials, equipment cleaning, using principles of ICH Q2 guideline. The appropriate validation reports should be accompanied with validation protocols and corresponding raw data (chromatograms; titrator, balance and other equipment printouts where possible), as well as result calculations and evaluation to ensure a necessary level of data traceability and data integrity as required by GMP. • Report on API forced-degradation and stress-testing studies (in the quality system, and according to guidelines requirements). • Documentation on necessary in-house reference standards of impurities, intermediates and API, including their specifications and methods of analysis; and information about commercially available and used non-pharmaceutical standards and/or samples (vendor, CoA, characterization data). • Results and CoA of testing samples of API, intermediates, raw materials, recovered materials and in-process control by validated analytical methods from lab. scale and kilo-lab studies.		
5.	Task 5. Specification package • Package should include justified Specifications for the API, intermediates, raw materials (incl. reagents, solvents, catalysts), recovered materials and other relevant materials used for manufacturing process, as well as should include justifications for all specifications taking into account ICH guidelines requirements. • <u>Specification for API</u> should be in compliance with requirements of guidelines ICH Q6A, Q3A, Q3C, Q3D, M7, as well as in compliance with general requirements of Ph.Eur. and US Pharmacopoeias, and should include control of at least the following quality attributes:		

	- Appearance / Description; - Identity (min. two different instrumental methods (e.g. IR and UV), plus polymorphic identity by XRPD); - Polymorphic impurity content by XRPD, with justified limit (not necessary if pure form is steadily produced and other forms are not detected, and there is a rationale for this and a report); - Assay (HPLC); - Related substances content (known, unknown and total including degradation impurities with limits defined in accordance with ICH Q3A guideline); - Residual solvents content (with limits in accordance with ICH Q3C guideline); - Potential genotoxic/mutagenic/N-nitrosamine impurities content (depending on results of genotoxic/mutagenic/N-nitrosamine impurities risk assessments and carry-over (fate & purge) study results, and with limits in accordance with ICH M7 guideline and recommendations for N-nitrosamines from EMA and FDA); - Elemental impurity/ies content (depending on results of elemental impurities risk assessments and carry-over, and with limits in accordance with ICH Q3D guideline); - Loss on drying and/or Water content (with justified limits); - Solubility; - Clarity of solution; - Sulphated ash / Residue on ignition (NMT 0.10 %); - Particle size distribution, by laser light diffraction; - Microbiological quality (limits for non-sterile APIs); - Other critical quality attributes if relevant (e.g., residual anions content, bulk density tapped and untapped, flowability, crystal morphology); - Definition of storage conditions and packaging, as well as retest date based on stability and forced-degradation study results. • Specifications for critical regulatory starting materials (RSMs) should be in compliance with requirements of ICH Q11 guideline, as well as in compliance with general requirements of Ph.Eur. and US Pharmacopoeias for test methods, and should include control of at least the following quality attributes: - Appearance / Description; - Identity (min. two different instrumental methods (e.g. IR and UV));		
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	- Assay (with justified limits); - Related substances content (known, unknown and total with justified limits as a results of impurities carry-over studies); - Residual solvents content (if relevant, and with justified limits as a results of impurities carry-over studies); - Potential genotoxic/mutagenic/N-nitrosamine impurities content (if relevant, and with justified limits as a results of impurities carry-over studies according to ICH M7 and EMA/FDA guidances on N-nitrosamines); - Elemental impurity/ies content (if relevant, and with justified limits as a results of risk assessment according to ICH Q3D); - Loss on drying and/or Water content (with justified limits); - Sulphated ash / Residue on ignition (with justified limits); - Other critical quality attributes if relevant (e.g., cation content, anion content, pH of solution, etc.); - Definition of storage conditions and packaging, as well as retest date based on stability studies results. <u>In addition to the proposed and justified specification, a technical package from the manufacturer/supplier must be provided for each purchased RSM (produced by third party), which must necessarily include a chemical scheme of Route of Synthesis, Specifications, Analysis methods, Stability Studies, a Brief Description of the manufacturing process and its block diagram, a list of all used starting and auxiliary materials, reagents, solvents, catalysts; discussion and characterization on impurities and their carry-over to RSM and control in RSM (organic impurities, inorganic and elemental impurities, residual solvents, mutagenic impurities, N-nitrosamines), as well as additional certificates for the site (for example, GMP) and confirmations of GMP audits from European, American or local agencies, if any.</u> • <u>Specifications for isolated intermediates</u> should be in compliance with requirements of ICH Q11 guideline, as well as in compliance with general requirements of Ph.Eur. and US Pharmacopoeias for test methods, and should include control of at least the following quality attributes: - Appearance / Description; - Identity (min. two different instrumental methods (e.g. IR and UV));		
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			- Assay (with justified limits); - Related substances content (known, unknown and total with justified limits as a results of impurities carry-over studies); - Loss on drying and/or Water content (with justified limits); - Optional: other critical quality attributes if relevant (e.g., residual solvents content, potential genotoxic/mutagenic/N-nitrosamine impurities content, cation content, elemental impurity/ies content, anion content, pH of solution, etc.); - Definition of storage conditions and packaging, as well as retest date based on stability studies results. • <u>Specifications for organic reagents, non-critical raw materials, solvents should be in compliance with requirements of ICH Q11 guideline, as well as in compliance with general requirements of Ph.Eur. and US Pharmacopoeias for test methods, and should include control of at least the following quality attributes:</u> - Appearance / Description; - Identity; - Assay (with justified limits) or Chromatographic purity; - Related substances content (known, unknown and total with justified limits as a results of impurities carry-over studies); - Loss on drying and/or Water content (if relevant, with justified limits); - Other critical quality attributes if relevant; - Definition of storage conditions and packaging, as well as retest date based on specifications or information from suppliers/manufacturers. • <u>Specifications for inorganic reagents and catalysts should be in compliance with requirements of ICH Q11 guideline, as well as in compliance with general requirements of Ph.Eur. and US Pharmacopoeias for test methods, and should include control of at least the following quality attributes:</u> - Appearance / Description; - Identity; - Assay (with justified limits); - Critical quality attributes showing catalyst activity (for catalysts); - Other critical quality attributes if relevant; - Definition of storage conditions and packaging, as well as retest date based on specifications or information from suppliers/manufacturers.		
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	• <u>Specifications for recovered materials</u> (e.g. recovered solvents, intermediates or crude API) must match the specifications for these materials from the main production process (e.g. specification for recovered solvent has to be the same as for commercial fresh solvent). If the quality of the recovered material does not correspond to the quality specification of this material from the main process, then a written justification for the use of such recovered material should be provided in terms of the consistency of the quality of the final product, carry-over of impurities, production process robustness and its reproducibility, as well as the safety of the production process. The specification of the recovered material must be accompanied by the results of analysis and CoAs obtained during the development of the technology and production of the kilo-lab batches. • <u>Quality specifications of commercial raw materials</u> created in accordance with the requirements of this technical specification (included in the package and proposed for technology transfer) have to be confirmed by suppliers/manufacturers and used by them for quality control and release of corresponding raw materials. Statements from suppliers/manufacturers have to be provided that supplier/manufacture use corresponding specification and test methods for quality control and release of the raw material, and for issuing CoAs.		
6.	Task 6. Impurity characterization package • Report on characterization data of known related substances in the API (including nature and source of impurity, actual content of the impurities in the API, proposed and justified limits according to ICH Q3A, chemical scheme of formation and classification of impurities (process-related, degradation, etc.), identification data by NMR ¹H and ¹³C, MS and IR spectra with signal assignments, UV spectra, other relevant identification techniques). • Report on carry-over of impurities study including: - Description and results of spiking experiments for justifying the quality specification limits for intermediates and raw materials, and for in-process control; - Calculation of purge factors (theoretical and/or experimental) and conclusion about fate and purge of possible impurities including organic, genotoxic / mutagenic impurities, N-nitrosamines, residual solvents, etc. • Risk assessment of elemental impurities for kilo-lab batches of the API according to ICH Q3D principles.		

	• Risk assessment of N-nitrosamine impurities for kilo-lab batches of the API according to EMA guidance and recommendations. • Risk assessment of genotoxic / mutagenic impurities for kilo-lab batches of the API according to ICH M7 principles and EMA guidance and recommendations (based on <i>in silico</i>, databases and literature data, results of Ames tests). • Samples of standards of known specified impurities in the API, intermediates, raw materials (including potentially mutagenic impurities) with CoA and characterization data. Contacts of supplies of these impurities samples/standards, or synthetic procedures for in-house synthesis of these impurities with corresponding qualification data. • Report on toxicological qualification of related substances and organic impurities if the proposed production technology does not allow obtaining API with an impurity content below the qualification limits according to ICH Q3A guideline requirements.		
7.	Task 7. Technology Transfer (TT) of API • Before the start of the TT Applicant must provide detailed requirements of equipment: - Provide specifications for any new or modified equipment required for the synthesis route. This should include reactor types, filtration systems, drying units, etc. - Detail requirements for control systems, including automation, monitoring, and data logging systems necessary to control and optimize the process. - Detail the requirements for the receiving facility. - Negotiate on equipment taking into account the technological capabilities and equipment of the Sponsor. • Before the start of the TT, ensure the supply of the selected Key Intermediate produced under the GMP in the quantities required for the TT, and also provide information on manufacturers/suppliers of other necessary raw materials for TT for a timely order. Batch size for TT – approx. 10 kg. • Before start of TT, ensure the supply of required reference standards, impurity standards and consumables for Quality control of manufacturing process and final API.		

	• Protocols for the transfer of developed and validated analytical methods from Applicant to the Sponsor's QC (by comparative testing (AMT) or co-validation techniques). Applicant must define the performance metrics (acceptance criteria) to evaluate the success of the Analytical Method Transfer, including method repeatability, variance and other parameters critical for successful method employment. • Support on reproducibility studies for synthetic process at Sponsor's R&D laboratory (irreproducibility means that the Tasks and/or subtasks of this Technical Specification regarding the synthesis process are not fulfilled by the applicant). • Collection of analytical and process data for pilot batches. Report about pilot production. Update of technology description and manufacturing protocols (if necessary). Optimization of crystallization to obtain pure polymorphic form of API with defined PSD (if necessary). • Technology Transfer should: - Define the performance metrics to evaluate the success of the technology transfer, including batch consistency, yield, purity, and compliance with regulatory requirements. - Clearly outline the acceptance criteria for process validation, scale-up batches, and final product quality; - Provide Technology Transfer protocol; - Review and correct production protocols / batch records for TT at sponsor's site; - Provide on-site support in the process of TT to adapt the production process to the sponsor's production equipment - Assessment of reproducibility when transferring technology (both synthesis and analytics), assistance in solving problems. If the transferred technology is not reproduced at Sponsor's site for reasons related to insufficiently developed technology, then the necessary technology updates and improvements is carried out at the expense of the developer. • Define the payment structure based on milestones, with payment due upon successful completion of each phase.		
8.	Task 8. Key Intermediate commercial supply • Documentation of Key Intermediate:		

	- Ensure that specifications for intermediate/-s are well-defined, including purity, identity, and content. These specifications should be derived from validated analytical methods and in compliance with pharmacopoeia standards or internal specifications as well as in line with ICH and GMP requirements. - Document the required specifications and control methods for all starting materials used in the manufacture of the API, including intermediates, excipients, and raw materials. - Documentation must outline the QC testing requirements for all raw materials and intermediates, including any in-process controls. - Documentation on QC testing of intermediate/-s and raw materials including Analytical Methods, validations, Quality Specifications. - Risk Assessment Reports of intermediate and starting materials for – N-nitrosamine presence, genotoxic impurities according to ICH M7 and elemental impurities according to ICH Q3D. - Provide Certificate of Analyses of intermediate and starting materials (3 batches). - Documentation of the storage conditions (temperature, humidity, etc.) required for intermediates to maintain their quality and stability. - Readiness to undergo GMP audits as the site for the production of the first stages of the API. • Commercial price offer (should be provided within this offer): - Price should be expressed in EUR/ kg (or USD/ kg); - Price should be given at least for two levels (50 kg, 100 kg) and optimal amount; • Lead time (should be provided within this offer): - Lead time should be expressed in weeks; - Incoterm should be clearly indicated; Deliverables: - Supply conditions and clearly defined pricing of Key Intermediate for API synthesis. Supporting documentation for Key Intermediate for API dossier (e.g. documentational package in a form of secondary ASMF including all information necessary for creation of Applicant Part and Restricted Part of API dossier)		
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9.	Costs of raw materials and other		Overall price without VAT (EUR)		

Validity term of the Offer - _____.

Deadline for performing the work - _____.

Name, Surname
 Position
 Date
 Signature