**Quality Assurance Agreement QA-YYYY-000**

Between Grau Pharma GmbH (Jordangasse 7/12, 1010 Vienna, Austria) hereafter referred to as „CUSTOMER“

And

*“Product supplier/Service provider” (Address; Town; Country)* hereafter referred to as *“Short name”* or „SUPPLIER“

Hereafter referred to collectively as “Contract partners.”

1. **Definitions**

**Active Pharmaceutical Ingredient (API)**: Any substance or mixture of substances intended to be used to manufacture a drug (or: medicinal) product. When used in the production of a drug, it becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or another direct effect on the diagnosis, cure, mitigation, treatment, or prevention of diseases or to affect the structure or any function of the body of man or animals.

**Adverse trend**: A trend in the values of any measure of the quality of a product or process outside the capability of the usual standard or indicates a reasonable probability that the product will fail to comply with specifications before the end of its assigned shelf-life or retest period.

**Agreement**: Arrangement undertaken by and legally binding on parties.

**(Governmental or Regulatory) Authority**: Any court, tribunal, arbitrator, agency, legislative body, commission, official or other instrumentality of (a) any government of any country, (b) a federal, state, province, or other political subdivision thereof, or (c) any supranational body including without limitation the European Medicines Agency (EMA).

**Business day**: Any day of the week other than Saturday, Sunday, or day on which the party is required to take action is regularly closed for business, i.e., Monday to Friday (European working hours) except any official national or regional bank holidays or shut down of the plant.

**CEP**: A certificate issued by the European Directorate for the Quality of Medicines stating the Product complies with the European Pharmacopoeia monograph and/or Transmissible Spongiform Encephalopathy (TSE) requirements. Also known as “CoS” = Certificate of Suitability.

**Certificate of Analysis**: A document identified as such, provided by the supplier, signed by its Responsible Person, or produced by a computer system that offers a degree of control equivalent to that given by a signature, which sets forth the analytical test results obtained from testing of a representative sample, against the specifications for the batch to be delivered.

**Certificate of Conformance**: A document identified as such, provided by the supplier and signed by a nominated representative of its Quality Unit, or produced by a computer system that offers a degree of control equivalent to that given by a signature, which certifies that each batch of product was produced and tested in compliance with the agreed specifications, GMP, and the relevant pharmacopeial monographs, as applicable, also known as Certificate of Compliance.

**Contract**: Business agreement for the supply of goods works performance work at a specified price.

**Contract Manufacturer**: Performance of some aspect of manufacture, under a contract, on behalf of the original manufacturer.

**Critical deviation**: A departure from an approved instruction, a standard operation, a predefined critical parameter, or an unanticipated event that could have an adverse impact, respectively, on the final substance quality and ability and/or characteristics.

**Customer**: The company or organization receiving the product/service once it has left the supplier’s control, including users and distributors.

**Data Integrity**: The extent to which all data is complete, consistent, and accurate throughout the data lifecycle. Data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA).

**Distributor:** Any party in the distribution/supply chain starting from the point at which an API or intermediate is transferred outside the control of the original manufacturer’s material management system, including parties involved in trade and distribution, such as (re)processors, (re)packagers, transport and warehousing companies, forwarding agents, brokers, traders, and suppliers other than the original manufacturer.

**DMF:** Drug Master File. The supplier’s dossier for providing confidential information to a regulatory authority about facilities, processes, or articles relating to the product (usually an API) used in the manufacturing, processing, packaging, and storing of one or more drugs (or: medicinal) products.

**GDP**: Good Distribution Practice. GDP deals with the distribution of products, including requirements for purchase, receiving, storage and export. GDP regulates the movement of products from the manufacturer’s premises to the end user, or to an intermediate point by using transport methods.

**GMP**: Good Manufacturing Practice. Requirements for the Quality System under which drug   
(or: medicinal) products and their (active) ingredients are manufactured. **Current Good Manufacturing Practice (cGMP):** this is the applicable term in the United States and European Union of this Agreement, the terms GMP and cGMP are equivalent.

**Immediately**: Generally, no more than twenty-four (24) business hours. This period may be exceeded due to events or circumstances beyond the reasonable control of the responsible party.

**Laws**: All laws, statutes, rules, regulations (including, without limitation, GMPs, NDA regulations, and other relevant provisions enforced by any applicable governmental authority), ordinances, and other pronouncements having the binding effect of the law of any governmental authority.

**Manufacturing License**: Concerning a country, any regulatory authorization red to manufacture one or more products or classes of products as granted by the relevant governmental authority.

**Material Safety Data Sheet (MSDS/SDS):** A document containing information on the potential hazards (health, fire, reactivity, and environmental) and how to work safely with the chemical product. MSDS also contains information on the use, storage, handling, and emergency procedures all related to the hazards of the material

**Non-conformance**: Departure of a quality characteristic from its intended level or state, such as to cause an associated product or activity not to comply with its specification, GMP, marketing authorization, or applicable law.

**OOE**: Out-of-expectation. A value obtained still meets the set requirements but significantly differs from the previous values or former trend.

**Original Manufacturer**: Person or company manufacturing product.

**Product Quality Review (PQR)**: The PQR is an assessment to verify the operational consistency of a process based on results trending and non-conformances.

**Promptly**: Generally, no more than three (3) business days. This period may be exceeded due to events or circumstances beyond the reasonable control of the responsible party.

**Quality Agreement**: A legally binding agreement mutually negotiated and concluded between (the Quality Departments of) API/intermediate manufacturers and their Customers. It is intended to define, in a formalized manner, responsibilities relative to quality tasks to assure the manufacture, supply and use, of product. It may also include commitments between the parties regarding (a) the provision of information, documents, or samples, and communication and notification rules including contacts.

**Quality Incident**: An incident relating to an issue or defect that is not necessarily detected by the specification parameters but could potentially result in a non-conformance. A “critical” quality incident is a defect or fault that makes a product unsuitable for use and could in a recall, retrieval or withdrawal.

**Record**: Document, stating results obtained and providing evidence of activities performed. The medium may be paper, magnetic, electronic or optical, photography, etc.

**Responsible Person**: The person(s) within the Quality Unit at the supplier who is accountable for releasing batches of product.

**Sample**: A part or parts of the product taken to show the quality of the whole.

**Sub-Contractor:** A third-party contractor, engaged and qualified by the supplier or original contract acceptor to perform any part of the supplier’s or initial contract acceptor’s GMP obligations under the License, Supply, or Quality Agreements.

**Supplier:** Person or company providing products or services on request. For this Agreement, a supplier is the (original) manufacturer supplier or another legal entity that supplies the product. In general, suppliers may also be traders or distributors.

**Supply chain:** For this Agreement, the supply chain is defined as all steps in the entire chain of distribution starting from the point at which products are transferred outside the control of the original manufacturer’s product management system downstream to the final user(s).

**Timely manner:** As soon as can be expected considering manufacturers' typical operations and processes, the defined responsibilities, and the agreed communication pathways.

1. **Contractual basis**

The following basis must be considered for this contract:

* 1. In providing the contractually agreed services per **Appendix 01** “List of contractually agreed *products/ services*,” consider the accepted pharmaceutical rules and all relevant legal requirements at the time of the execution, in particular *(e.g., and EU-GMP-guidelines, ISO-Norm: please adapt to relevant legal requirements)*.
  2. *Add for contract laboratories, otherwise delete (Short name)* is under the obligation to comply with all valid legal requirements in disposing of all samples, waste and spillage. The disposal of the product rests may only proceed after consultation with «CUSTOMER“ and in accordance with **Appendix 02** “CUSTOMER and SUPPLIER Matrix of responsibilities”.
  3. *(Short name)* and «CUSTOMER“ name the persons listed in **Appendix 03** “CUSTOMER and SUPPLIER contacts” as contact partners for all questions. Changes and alterations must be communicated in writing immediately.

1. **Contractual object**
   1. This general Quality Assurance Agreement is the legal confirmation of the general conditions and processes between the CUSTOMER and SUPPLIER which are necessary in order to achieve the pursued quality objectives and comply with the legal requirements.
   2. CUSTOMER requests SUPPLIER products/services according to CUSTOMER’S needs. All contractual products / services are defined in the **Appendix 01** “List of contractually agreed products / services”.
   3. The clauses of this contract are valid for all assignments .*(please adapt) in order to test drugs or other services bound by GMP* which are issued after the signing of this contract and before its termination. *The analyses or services (please adapt)* will be carried out according to the state of medical science and technology.
   4. The commercial aspects are defined in a separate contract. The assignment of individual *services / product deliveries* takes place through a separate order from CUSTOMER each time.
2. **Liability**
   1. In the event that CUSTOMER makes use of the final product proceeding from the contractual service and damage that falls under medical liability insurance occurs, and is derived from a flawed service of *”Short name”*, then *“Short name”* is liable for the produced personal and product damages.
3. **Confidentiality**

*(In case an already signed confidentiality agreement exists).*

* 1. The mutual obligations of the contract partners to confidentiality and to not use the information are contractually defined in the Confidentiality agreement (NDA No. *xxxx*). The Contract partners herewith agree that the provisions of the NDA No. *xxxx* remain in full effect during the term of this Quality Assurance Agreement.

*(If no confidentiality agreement was signed before, please delete:)*

1. *“Short name”* is obligated, regarding all information and documentation and all further contents of any given communications with CUSTOMER, to keep strict confidentiality and use it exclusively for the purpose of evaluating the feasibility of the potential order. In the event that third parties need to be involved in the evaluation, their participation requires the approval of the CUSTOMER. In case of approval, SUPPLIER must also sign a confidentiality agreement with the third party, in turn obliging them to confidentiality towards further third parties. SUPPLIER must present the confidentiality agreement ahead to CUSTOMER. Insofar as third parties are involved in the evaluation, these may not entrust further third parties with the evaluation or development of an offer; this is also valid if the further third parties are obligated to confidentiality. Documents disclosed to third parties must be labeled as confidential.
2. use it exclusively for the purpose of this contract,
3. not make any commercial use of it,
4. not include it as part of intellectual property, and
5. only make it available to employees that require it for the purpose of this contract and who have before been bound to confidentiality, including time after they cease to work for the company, as long as this is legally permitted,
6. destroy or return it to CUSTOMER in case a contract between the two partners should not come to happen. This obligation extends to all handwritten notes, sketches, electronic data entries etc. produced by SUPPLIER.

The place of jurisdiction for disputes resulting from this contract applied as defined in the *(MSA / MPA)*

This agreement is composed of xx (…) pages including xx (….) Appendixes(n):

Appendix 01: List of contractually agreed products/services

Appendix 02: CUSTOMER and SUPPLIER Matrix of responsibilities

Appendix 03: CUSTOMER and SUPPLIER contacts

These appendixes are an integral part of the contract and subject to the same regulations. In case of discrepancies between the contract and the appendixes, the conditions of the contract take priority.

|  |  |
| --- | --- |
| **«CUSTOMER“**  ***Long name / legal entity (adapt)*** | |
| Place |  |
| Date |  |
| Signature |  |
| Function |  |
| First name, last name in block letters |  |

|  |  |
| --- | --- |
| **«SUPPLIER“**  ***Long name / legal entity (adapt)*** | |
| Place |  |
| Date |  |
| Signature |  |
| Function |  |
| First name, last name in block letters |  |

**Appendix 01 to QA-YYYY-000: List of contractually agreed products/services**

*(please delete not applicable sections)*

«CUSTOMER“ *(Address, Town, Country)* and *“Short name” (Address, Town, Country)* agree on the following contractual products:

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Contractual products** | | |
| **«CUSTOMER“ item no.** | **Designation** | *“Short name“* **item no.** | **Units** |
|  |  |  |  |
|  |  |  |  |

*or*

«CUSTOMER“ *(Address, Town, Country)* and *“Short name ” (Address, Town, Country)* agree on the following services:

|  |  |
| --- | --- |
| **Services** | |
| **No.** | **Scope of service** |
|  |  |
|  |  |

*or*

«CUSTOMER“ *(Address, Town, Country)* and *“Short name” (Address, Town, Country)* agree on the following tests:

|  |  |
| --- | --- |
| **Contract laboratories / Scope of service** | |
| **Designation of product intended for external testing** | **Specification / Method (e.g. Pharmacopeial monograph, reference to documents if possible)** |
|  |  |
|  |  |
|  |  |

**Appendix 02 to QA-YYYY-000:** **CUSTOMER and SUPPLIER Matrix of responsibilities**

[ C = CUSTOMER; S = SUPPLIER, N/A = Not applicable]

|  | **Responsibilities** | C | S | N/A |
| --- | --- | --- | --- | --- |
| **1** | **Applicable GMP Standard / Regulatory Compliance** |  |  |  |
| 1.01 | Manufacturing PRODUCT in compliance with the applicable Current Good Manufacturing Practices (CGMPs). For the purposes of this agreement, CGMP shall mean the principles (i) described in the currently valid ICH Q7 Guide (incl. the currently valid Q&A) as well as the ICH Q9 and Q10 Guidelines, (ii) promulgated by any governmental or regulatory authority having jurisdiction over the manufacture of the PRODUCT, in the form of laws or guidance documents, where the guidance documents are to be implemented within the pharmaceutical industry for such PRODUCT. |  |  |  |
| 1.02 | Adhering to approved registration documentation (Marketing Authorization, NDA, IND, DMF, CEP, etc., as applicable) |  |  |  |
| 1.03 | Maintaining valid manufacturing license(s), as applicable |  |  |  |
| 1.04 | Maintaining site master file complying with the applicable authority requirements (e.g. EU GMP Guide Part III) |  |  |  |
| 1.05 | Establishing synthesis scheme (including definition of API starting materials) |  |  |  |
| 1.06 | Providing test procedures, stability reports, statements, and other quality or regulatory documents as mutually agreed between the parties (see also 8.02, 10.04 and 12) |  |  |  |
| 1.07 | Optional: SUPPLIER carries out a quality management system in accordance with § 3 AMWHV. This system complies with the currently valid EU guidelines for a Good Manufacturing Practice for pharmaceuticals. SUPPLIER has registered its activity in accordance with § 67 AMG to the responsible government office and has appropriate premises and facilities for the intended tests. Therefore, SUPPLIER fulfils the requirements to be able to offer the service of testing pharmaceuticals according to § 14 (4) AMG. |  |  |  |
| 1.08 | Optional: SUPPLIER is subject, among others, to inspection by the (district) government of *(please complete).* (Pharmaceutical tests), by the public health office (handling of pathogens according to § 44 of the German infection protection law,) and by the district’s veterinary inspection office *(please complete)* as well as by the DAKKS (German certification office, Deutsche Akkreditierungsstelle GmbH) for certification in accordance with DIN EN ISO/IEC 17025. |  |  |  |
| 1.08 | Optional: SUPPLIER informs CUSTOMER about Changes that limit the reports according to § 67 AMG or the conditions according to § 14 (4) AMG as well as the above listed permits and accreditations / certificates are informed by *(short name)* immediately to «CUSTOMER“. |  |  |  |
| **2** | **Change Control** |  |  |  |
| 2.01 | SUPPLIER shall have a documented and effective change control system in place. SUPPLIER shall inform CUSTOMER of any significant changes to the manufacture of PRODUCT, which may have an impact on the quality of supplied PRODUCT, and/or on any regulatory applications related to PRODUCT. SUPPLIER shall notify CUSTOMER within a reasonable time, prior to implementation, to allow CUSTOMER to assess the potential impact of the change upon the PRODUCT supplied or its use by CUSTOMER. |  | X |  |
| 2.02 | The implementation of changes requiring authorities’ pre-approval or changes with a demonstrable effect on the PRODUCT quality shall not occur until the CUSTOMER has given written approval. |  |  |  |
| 2.03 | SUPPLIER shall only supply CUSTOMER with PRODUCT described in any applicable, current DMF and/or CUSTOMER's existing regulatory filings until PRODUCT manufactured following such change is permitted under the regulatory filings therefore or if approved in writing by CUSTOMER to receive PRODUCT prior to regulatory approval (e.g., for trial production). SUPPLIER shall inform CUSTOMER about the start of PRODUCT supplies with the new quality after the change (batch number, date). |  |  |  |
| 2.04 | CUSTOMER has the final responsibility for ensuring regulatory compliance for the finished product brought to the market. |  |  |  |
| 2.05 | CUSTOMER shall provide SUPPLIER with information about its regulatory filings if they differ from those supplied by SUPPLIER to CUSTOMER. | X |  |  |
| 2.06 | For those changes required to comply with applicable laws and regulatory authority requirements concerning PRODUCT, SUPPLIER shall notify CUSTOMER of such requirements after SUPPLIER becomes aware of the need for such changes, and vice versa. |  |  |  |
| 2.07 | Minor changes which are not expected to have an impact on PRODUCT quality or the regulatory filings of CUSTOMER shall be processed by SUPPLIER’s change control system. |  |  |  |
| 2.08 | CUSTOMER undertakes to submit within a reasonable period of time all necessary change notifications to all competent authorities in full compliance with the applicable regulations, respectively, and to inform SUPPLIER of the receipt of the necessary acknowledgment of the validity of the notification and, depending on the type of change, the acceptance or approval of the change by the competent authorities. |  |  |  |
| **3** | **Regulatory Documents** |  |  |  |
| 3.01 | SUPPLIER is responsible for maintaining the appropriate registration documents for the PRODUCT (i.e. dossier for CEP, DMF or equivalent) in countries where these documents have been submitted already. |  |  |  |
| 3.02 | Upon mutual agreement with CUSTOMER, SUPPLIER will prepare and submit registration documents in countries where SUPPLIER has not yet registered the product. |  |  |  |
| 3.03 | SUPPLIER is responsible for all regulatory contacts with the relevant regulatory authority with jurisdiction over the PRODUCT. |  |  |  |
| 3.04 | SUPPLIER will provide current information to CUSTOMER Affiliates reasonably requested for submission of any regulatory dossier by CUSTOMER Affiliates for finished drug products made from PRODUCT. Such information will include either access to CEP (including the appropriate stability data for the respective PRODUCT, if no retest date is defined in the CEP), or applicants’ part to DMF, or equivalent. |  |  |  |
| 3.05 | CUSTOMER Affiliates are responsible for submitting the regulatory dossier for the Marketing Authorization Application associated with any finished drug product made from the respective PRODUCT. Such regulatory dossier, as it pertains to SUPPLIER, will refer to SUPPLIER’s CEP, DMF or equivalent, where applicable. |  |  |  |
| **4** | **Audits** |  |  |  |
| 4.01 | SUPPLIER shall allow –upon signature of a special (personal) confidentiality agreement– CUSTOMER or its representatives (may also be a 3rd party auditor) to carry out on-site audits by appointment. SUPPLIER shall permit all reasonable access to the manufacturing, packaging, warehousing, and laboratory areas related to the manufacture of PRODUCT, including pertinent documentation. Any such audit shall take place during normal business hours and must not interfere with SUPPLIER’s manufacturing operations. Alternatively, existing 3rd party audit reports may be used, if agreed by all parties. |  |  |  |
| 4.02 | CUSTOMER shall notify SUPPLIER of its audit request at least 3 months in advance of the desired audit date. |  |  |  |
| 4.03 | The results of the audit and the observation(s) shall be sent to the SUPPLIER by means of a written report. |  |  |  |
| 4.04 | SUPPLIER shall send to the customer a formal response to the audit observations including any relevant CAPAs and timelines for implementation. |  |  |  |
| 4.05 | The audit frequency shall depend upon the results of the previous audit(s) and the quality performance of the SUPPLIER. In the absence of critical quality incidents, the frequency shall be not more than once every three (3) years. |  |  |  |
| 4.06 | Upon request by regulatory authorities or as required by applicable law, CUSTOMER may disclose all or part of its audit report to regulatory authorities without prior approval by SUPPLIER. |  |  |  |
| 4.07 | In case of significant quality incidents or critical cGMP, deficiencies SUPPLIER will allow CUSTOMER to conduct “for-cause” audits at SUPPLIER’s facilities until the issue is resolved to both parties’ mutual reasonable satisfaction. |  |  |  |
| **5** | **Authority Inspections** |  |  |  |
| 5.01 | SUPPLIER shall promptly notify CUSTOMER of any regulatory or cGMP violations (e.g. FDA Warning Letter or suspension/withdrawal of one or more CEPs) identified during authority GMP inspections and impacting the quality of PRODUCT intended to be shipped to CUSTOMER and/or potentially affecting the ability of SUPPLIER to produce or ship the PRODUCT. |  |  |  |
| **6** | **Data Integrity** |  |  |  |
| 6.01 | SUPPLIER agrees to have procedures in place to ensure quality-relevant data is attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA); that it can be traced to its source and that it is readily available during regulatory inspections. |  |  |  |
| 6.02 | SUPPLIER further agrees to notify CUSTOMER of any breach to the integrity of the data affecting the quality or the safety of any PRODUCT batches already shipped to CUSTOMER, as soon as possible, but not to exceed two (2) business days after becoming aware of the event. |  |  |  |
| **7** | **Specifications** |  |  |  |
| 7.01 | Setting standard specifications for PRODUCT and intermediates |  |  |  |
| 7.02 | Mutually agree upon specification for PRODUCT, which may include customer-specific items |  |  |  |
| 7.03 | *[Optional (if not managed in a separate document): Specifications for PRODUCT are detailed in the Appendix.]* |  |  |  |
| **8** | **Laboratory Controls** |  |  |  |
| 8.01 | Sampling and testing of intermediates and final PRODUCT |  |  |  |
| 8.02 | SUPPLIER shall provide to CUSTOMER any in-house methods, including validation reports, used for testing according to the agreed specifications (where there are no compendial methods). |  |  |  |
| 8.03 | Compendial analytical methods must be verified and all others must be validated prior to their use for release of commercial PRODUCT batches. |  |  |  |
| 8.04 | SUPPLIER shall use adequately qualified or certified reference standards. |  |  |  |
| 8.05 | All reference standards should be stored in accordance with the SUPPLIERS recommended storage conditions and used within their given expiry or retest date. |  |  |  |
| 8.06 | *[Optional: SUPPLIER shall provide to CUSTOMER reasonable quantities of any non-compendial, commercially not available reference standards necessary to perform the tests included in the PRODUCT specification.]* |  |  |  |
| 8.07 | SUPPLIER will store PRODUCT retention samples, sufficient to perform at least two (2) full specification analyses (see Note 7.2), in containers that are equivalent to or more protective than the commercial packaging. Samples are to be retained for at least one (1) year after the expiry or retest date of the batch assigned by SUPPLIER or for three (3) years after distribution, whichever is the longer. |  |  |  |
|  | Samples handling |  |  |  |
| 8.09 | Instructions to take samples, execution of sampling, shipping of samples |  |  |  |
| 8.10 | Repackaging of samples |  |  |  |
| 8.11 | Decision on shipping and storage conditions of samples |  |  |  |
| 8.12 | Compliance with shipping conditions for samples |  |  |  |
| 8.13 | Compliance with storage conditions after reception by *“Short name”* |  |  |  |
| 8.14 | Storage of samples until the completion of testing |  |  |  |
| 8.15 | Proper destruction of samples after completion of testing |  |  |  |
|  | Testing |  |  |  |
| 8.16 | Availability of conforming specifications and testing methods |  |  |  |
| 8.17 | The setting of testing regulations |  |  |  |
| 8.18 | Validation of testing regulations |  |  |  |
| 8.19 | Verification of specifications and testing procedures for their conformity with the state of science and technology |  |  |  |
| 8.20 | Execution of tests following approved testing methods in conformity with the state of science and technology |  |  |  |
| 8.21 | cGMP conforming documentation of the test |  |  |  |
| 8.22 | Issuing of a test report |  |  |  |
| 8.23 | Information on OOS results, laboratory tests in case of OOS results |  |  |  |
| 8.24 | Information on discrepancies in testing |  |  |  |
| 8.25 | Evaluation of batches, batch release |  |  |  |
| 8.26 | Acquisition of commercially available appropriate reagents and media |  |  |  |
| 8.27 | Proper acquisition and storage of reference strains |  |  |  |
| 8.28 | Acquisition of commercially available standard substances |  |  |  |
| 8.29 | Providing reference substances that are not commercially available |  |  |  |
| 8.30 | Proper storage of standard substances |  |  |  |
|  | Method transfer |  |  |  |
| 8.31 | Method transfer of «CUSTOMER“ to *“Short name”* |  |  |  |
| 8.32 | Development of method transfer plans |  |  |  |
| 8.33 | Approval of method transfer plans |  |  |  |
| 8.34 | Execution of method transfer plans |  |  |  |
| 8.35 | Documentation of method transfer plans |  |  |  |
| 8.36 | Issuing method transfer reports |  |  |  |
| 8.37 | Approval of method transfer reports |  |  |  |
|  | Method validation |  |  |  |
| 8.38 | Validation of methods / revalidations |  |  |  |
| 8.39 | Development of validation plans |  |  |  |
| 8.40 | Approval of validation plans |  |  |  |
| 8.45 | Execution of validation tasks |  |  |  |
| 8.46 | Documentation of validation tasks |  |  |  |
| 8.47 | Issuing validation reports |  |  |  |
| 8.48 | Approval of validation reports |  |  |  |
| **9** | **Product Release** |  |  |  |
| 9.01 | Release of PRODUCT batches for delivery to CUSTOMER. |  |  |  |
| 9.02 | *[Optional: SUPPLIER will not ship any PRODUCT to CUSTOMER until the PRODUCT is released, unless prior written approval has been received from CUSTOMER to perform such a shipment under quarantine.]* |  |  |  |
| **10** | **Stability** |  |  |  |
| 10.01 | SUPPLIER has assigned retest dates (or expiry dates, where applicable), and storage and shipping conditions, based upon stability studies. |  |  |  |
| 10.02 | SUPPLIER is responsible for performing on-going stability studies for the PRODUCT. At least one batch per year should be tested to ICH requirements (a batch representing routine production; long-term storage conditions only). |  |  |  |
| 10.03 | SUPPLIER is responsible for performing appropriate stability studies on the PRODUCT arising from process changes. |  |  |  |
| 10.04 | SUPPLIER will provide stability data to CUSTOMER upon reasonable request (e.g., if required according to the applied registration procedure). |  |  |  |
| 10.05 | SUPPLIER will inform CUSTOMER if there are any adverse trends in the stability studies that could impact on current retest date/period. |  |  |  |
| **11** | **Certificate of Analysis / *[Conformance (optional)]*** |  |  |  |
| 11.01 | A Certificate of Analysis *[and a Certificate of Conformance (optional)]* are required for each batch of PRODUCT shipped to CUSTOMER. |  |  |  |
| 11.02 | The Certificates of Analysis *[and Conformance (optional)]* shall be dated and signed by a responsible person of the SUPPLIER’s Quality Unit, or it may be produced by a computer system, which provides a degree of control equivalent to that given by a signature. |  |  |  |
| 11.03 | The Certificate of Analysis states that the batch is suitable for release, and it must include – as a minimum – the SUPPLIER name and address, incl. telephone number Name and address of the original manufacturer, if the SUPPLIER is not the original manufacturer PRODUCT name and grade (if applicable), SUPPLIER batch/lot number, Reference to the agreed specification, Test parameters and corresponding specification requirements, Test results (numerical, where applicable) for each chemical, physical or microbiological test performed, Date of release and expiration or retest date of the PRODUCT |  |  |  |
| 11.04 | *[Optional: The Certificate of Conformance states that the subject lot was produced in accordance with the applicable DMF, CEP, or pharmacopeial monograph(s), and in compliance with all applicable GMP requirements. Certificate of Analysis and Certificate of Conformance may be issued as separate documents or combined into a single document, as appropriate.]* |  |  |  |
| **12** | **Certificates, Statements, and Declarations** |  |  |  |
| 12.00 | SUPPLIER shall provide the following certificates and statements at the approval of this Quality Agreement and any time these certificates are renewed: |  |  |  |
| 12.01 | cGMP certificate(s): Where not publicly accessible, SUPPLIER shall provide CUSTOMER with copies of the current GMP certificates or GMP licenses, pertaining to the manufacture of PRODUCT, issued by European or other local/national health authorities. |  |  |  |
| 12.02 | BSE/TSE\*: SUPPLIER shall provide to CUSTOMER a BSE/TSE certificate for PRODUCT in accordance with the EMEA Note for Guidance EMEA/410/01 (current revision). The certificate shall indicate if the PRODUCT is of human  or animal origin and if materials of human or animal origin are used during the manufacturing process of PRODUCT.. An updated BSE/TSE certificate must be issued after any change to the manufacturing process, which involves new raw materials, or raw materials that have been sourced from a different supplier. |  |  |  |
| 12.03 | Residual solvents\*: SUPPLIER shall provide to CUSTOMER a residual solvents statement for PRODUCT in accordance with the ICH Q3C guideline. An updated statement must be issued after changes to the manufacture of the PRODUCT, if applicable. |  |  |  |
| 12.04 | Elemental impurities\*: SUPPLIER shall provide to CUSTOMER a statement on metal residues for PRODUCT in accordance with the ICH Q3D Guidelines on elemental impurities and other applicable regulations. An updated statement must be issued after changes to the manufacture of PRODUCT, if applicable. |  |  |  |
|  | \*) If the CEP contains the required information on BSE/TSE, residual solvents or metal catalyst/reagent residues, then the CEP itself may be used instead of separate supplier declarations. |  |  |  |
| 12.05 | Importation into the EU: SUPPLIER shall ensure that a valid ‘written confirmation’ according to EU Directive 2011/62/EU, related to PRODUCT and signed by the competent local authority is available. SUPPLIER shall ensure that a copy of this ‘written confirmation’ will accompany every shipment of PRODUCT into the EU. SUPPLIER shall have a system in place to renew the ‘written confirmation’ with the competent local authority before expiry. SUPPLIER shall inform CUSTOMER immediately in case the “written confirmation’ is withdrawn by a competent local authority or the renewal is not completed before expiration. |  |  |  |
| **13** | **Product Quality Review and Quality Metrics** |  |  |  |
| 13.01 | SUPPLIER shall allow CUSTOMER to review the annual Product Quality Review (PQR) for the PRODUCT during an on-site audit. In case the PQR contains any proprietary customer-specific information, the entire file may not be available for review or shall be redacted, as appropriate. |  |  |  |
| **14** | **Retention of Records/Documentation** |  |  |  |
| 14.01 | SUPPLIER will store the original master batch records, the executed batch records, and all other original documentation that is related to the manufacture of substance and that is required to be maintained under cGMP, protected from destruction and unauthorized access, for at least one (1) year after the expiry or retest date of the batch assigned by SUPPLIER or for three (3) years after distribution, whichever is longer. |  |  |  |
| 14.02 | SUPPLIER will make the original records related to the manufacture of PRODUCT available for CUSTOMER during an on-site audit or by request. |  |  |  |
| 14.03 | Validation documents should be archived for as long as PRODUCT is supplied or for 7 years after the version became obsolete. |  |  |  |
| 14.06 | *[Optional: SUPPLIER develops documents (protocols, reports, etc.) in accordance with AMWHV and EU-GMP guidelines for all performed activities. SUPPLIER collects all underlying raw data (primary observations and measured numbers before evaluation/calculation).]* |  |  |  |
| 14.07 | *[Optional: SUPPLIER keeps the complete documentation according to the time period specified in § 20 AMWHV. Keeps the raw data and documents for all other services for 10 years after the issuing of the assignment.]* |  |  |  |
| 14.08 | *[Optional: After the above specified archiving period has expired, SUPPLIER is obliged to inform CUSTOMER and wait for its confirmation before raw data and documents are destroyed.]* |  |  |  |
| **15** | **Materials** |  |  |  |
| 15.01 | Setting specifications for materials (incl. API starting materials, raw materials, process aids, and packaging materials, as applicable). |  |  |  |
| 15.02 | Purchasing materials according to specifications |  |  |  |
| 15.03 | Sampling and inspecting or testing of incoming materials, as appropriate. Materials supplied by qualified vendors can be subject to reduced testing but a minimum ID testing (or visual examination of containers, labels, and documentation in case of hazardous or highly toxic raw materials) needs to be performed for each delivery and each lot. |  |  |  |
| 15.04 | Qualifying and monitoring material suppliers (with the exception of materials supplied by CUSTOMER). |  |  |  |
| 15.05 | SUPPLIER shall ensure that its material suppliers ship their goods on compliant pallets; i.e. in case wooden pallets are used, these should be marked as Heat Treated (HT). Any material that is received on a wooden pallet that does not meet these requirements shall be transferred to a compliant pallet. |  |  |  |
| **16** | **Manufacturing (incl. Qualification / Validation)** |  |  |  |
| 16.01 | Qualifying of equipment, utilities, and facilities |  |  |  |
| 16.02 | Validating the manufacturing process, cleaning procedures, analytical methods, and computerized systems |  |  |  |
| 16.03 | SUPPLIER shall allow CUSTOMER to review qualification and validation documentation for the PRODUCT during an on-site audit. |  |  |  |
| 16.04 | Analytical methods validation should be concluded prior to the release of the Process Validation batches. |  |  |  |
| 16.05 | SUPPLIER shall have appropriate control procedures in place to ensure that only authorized personnel has access to SUPPLIER’s manufacturing facilities. |  |  |  |
| **17** | **Reprocessing / Reworking** |  |  |  |
| 17.01 | Reprocessing of a PRODUCT batch is permissible if the reprocessing complies with the current regulatory dossier; the reason for the reprocessing has to be investigated and documented, respectively. |  |  |  |
| 17.02 | For any lots undergoing reprocessing, the SUPPLIER should consider the need to put the respective batch(es) on stability. |  |  |  |
| 17.03 | SUPPLIER has demonstrated that the reprocessed batch is of at least equivalent quality as a normal batch. |  |  |  |
| 17.06 | Reworking must be performed, if at all, according to the PRODUCT registration documents, if it is part of the dossier, or according to ICH Q7, chapter 14.3. CUSTOMER should be informed of such batches/lots. |  |  |  |
| **18** | **Highly Active Pharmaceutical Ingredients (HAPIs)** |  |  |  |
| 18.01 | SUPPLIER shall not conduct production and handling of highly sensitizing materials (such as penicillins or cephalosporins) in the equipment being used for the PRODUCT. Production of such materials in the same building being used for the PRODUCT is permitted only if performed in a closed and dedicated system. |  |  |  |
| 18.02 | In case material of an infectious nature or high pharmacological activity or toxicity (e.g., certain steroids or cytotoxic anti-cancer agents) is manufactured by the SUPPLIER in the same facilities as used for PRODUCT, validated inactivation and/or cleaning procedures should be in place, based upon a toxicological evaluation for the establishment of threshold values in relation to the products manufactured. |  |  |  |
| 18.03 | SUPPLIER shall inform CUSTOMER prior to the introduction of a HAPI in the same facilities where the PRODUCT is manufactured, if no HAPIs were produced before. |  |  |  |
| **19** | **Supplier qualification / Supplier Sub-contracting** |  |  |  |
| 19.01 | Regular risk-based SUPPLIER qualification based on Technical Visits, Audits results, a self-disclosure form assessment, and certificates. SUPPLIER qualifications are carried out on a regular basis according to CUSTOMER’s procedures. |  |  |  |
| 19.02 | SUPPLIER will use its established GMP systems for evaluation, qualification, approval, and maintenance/monitoring of all sub-contracted services with a GMP impact on the PRODUCT manufactured. |  |  |  |
| 19.03 | *[Optional: Previous written approval of new SUPPLIER’s Sub-Contractor prior to use]* |  |  |  |
| 19.04 | SUPPLIER will sign off relevant Quality Agreements with Sub-Contractors |  |  |  |
| 19.05 | SUPPLIER shall notify CUSTOMER of any change to approved, or introduction of new sub-contractor used for any GMP-relevant service if the regulatory filings of the PRODUCT are concerned. |  |  |  |
| 19.06 | SUPPLIER shall remain fully responsible for the quality of the materials or services provided by sub-contractors and for all commitments as agreed upon with this Quality Agreement. |  |  |  |
| 19.07 | SUPPLIER will allow CUSTOMER access to audit reports of its subcontractors during an audit. |  |  |  |
| **20** | **Packaging** |  |  |  |
| 20.01 | In addition to the requirements in ICH Q7 the following shall apply to the packaging of PRODUCT: The specifications for packaging materials including tamper evident seals must be in accordance with the regulatory documentation related to PRODUCT. |  |  |  |
| 20.02 | SUPPLIER shall apply suitable traceability measures to primary packaging materials such that the packaging material manufacturer’s batch can be traced from the batch of PRODUCT supplied. |  |  |  |
| 20.03 | *[Optional: SUPPLIER shall package the PRODUCT using the components, closures and tamper-evident seals as specified.]* |  |  |  |
|  | *( List other security measures here, as applicable)* |  |  |  |
| 20.04 | *[Optional: When primary packaging material is returned from CUSTOMER to SUPPLIER for reuse, SUPPLIER will validate the cleaning procedure(s) used to clean the packaging material.]* |  |  |  |
| **21** | **Labelling** |  |  |  |
| 21.01 | Labelling operations, including label printing and label reconciliation, should be done in a manner that prevents mislabeling and mix-ups. |  |  |  |
| 21.02 | Applicable regulatory requirements should be considered in order to permit shipments without delays or other issues (e.g. at customs). |  |  |  |
| 21.03 | *[Optional: SUPPLIER shall indicate the retest date on the PRODUCT label.]* |  |  |  |
| **22** | **Storage and distribution (incl. Supply Chain Traceability)** |  |  |  |
| 22.01 | SUPPLIER shall make commercially reasonable efforts to exclude, during packaging, storage, and shipping of PRODUCT, the possibility of deterioration, contamination, or mix-ups with any other material. |  |  |  |
| 22.02 | SUPPLIER shall comply with the following requirements in relation to the distribution of the PRODUCT: Distribution - until the agreed transition point - in accordance with the conditions specified by the manufacturer and in a manner that does not adversely affect their quality (ref. EU GDP 6.14.) Ability to recall the PRODUCT from the distribution network Quarantine PRODUCT with questionable quality Utilize tamper-evident seals on all packaging. All outbound shipments on wooden pallets must be on pallets that are marked as Heat Treated (HT). |  | X |  |
| 22.03 | SUPPLIER will qualify haulers and shipping agents used to transport the PRODUCT. |  |  |  |
| 22.04 | Where storage or transportation is contracted out, SUPPLIER or CUSTOMER (as to respective responsibilities), should ensure that the external service provider knows and follows the appropriate storage and transport conditions. There must be a written contract, which clearly establishes the duties of each party, and the contract acceptor should not subcontract any of the work entrusted to him under the contract without the contract giver’s written approval. |  |  |  |
| 22.05 | SUPPLIER will provide an up-to-date MSDS to CUSTOMER with each shipment or at least on an annual basis. |  |  |  |
| 22.06 | SUPPLIER shall comply with any applicable legal requirements in relation to the transportation of PRODUCT. |  |  |  |
| 22.07 | SUPPLIER will keep supply chain traceability records available and retained. |  |  |  |
| 22.08 | Upon reasonable request, SUPPLIER will provide information to CUSTOMER on the supply chain for PRODUCT between SUPPLIER’s manufacturing site(s) and CUSTOMER’s receiving site(s), including any transportation services or interim storage locations. |  |  |  |
| 22.09 | * Providing documentation to ensure supply chain traceability for each delivery of PRODUCT. This includes: reference to purchase order and date of supply name of PRODUCT, manufacturer’s batch number and quantity supplied name and address of SUPPLIER, or of the shipping agent and/or the consignee bills of lading, transportation and distribution records a certificate of analysis for each batch in the delivery |  |  |  |
| 22.10 | SUPPLIER will inform CUSTOMER on changes to the identified supply chain according to the established change control procedures. |  |  |  |
| 22.11 | If a delivered PRODUCT needs to be returned, SUPPLIER and CUSTOMER will agree on responsibilities and conditions prior to the return shipment. |  |  |  |
| **23** | **Deviations / OOS (incl. stability)** |  |  |  |
| 23.01 | SUPPLIER shall document all deviations and investigate OOS results and critical deviations. |  |  |  |
| 23.02 | In case of serious quality incidents observed only after the shipment of batches of PRODUCT to CUSTOMER, SUPPLIER shall promptly and appropriately notify CUSTOMER thereof. |  |  |  |
| **24** | **Complaints** |  |  |  |
| 24.01 | CUSTOMER shall inspect the goods upon delivery and promptly notify any defect or shortage to SUPPLIER. |  |  |  |
| 24.02 | All complaints related to the PRODUCT, regardless of source (e.g., consumers, doctors, pharmacists, sales representatives) will be communicated to SUPPLIER in writing. |  |  |  |
| 24.03 | SUPPLIER will respond to complaints by the CUSTOMER in a timely manner and according to formally agreed procedures. |  |  |  |
| 24.04 | SUPPLIER will inform CUSTOMER in a timely manner and in writing of the conclusions driven by the investigation performed and the corrective/preventive actions defined. |  |  |  |
| 24.05 | In case the investigation could not be finalized within 30 calendar days, SUPPLIER will provide an interim report to CUSTOMER. |  |  |  |
| 24.06 | CUSTOMER will make relevant information and samples of the affected PRODUCT batch(es)/lot(s) available in a timely manner to assist in the investigation of SUPPLIER (as appropriate). |  |  |  |
| 24.07 | SUPPLIER will inform CUSTOMER if any received complaint could also have a serious impact on batches supplied to CUSTOMER (i.e., the complaint constitutes a potential risk to patient’s health or safety). |  |  |  |
| **25** | **Recall** |  |  |  |
| 25.01 | Immediately after SUPPLIER has become aware of it, SUPPLIER will inform CUSTOMER of any serious quality issue that may result in a recall of supplied PRODUCT or finished drug product made thereof. |  |  |  |
| 25.02 | SUPPLIER and CUSTOMER consult and decide on roles and responsibilities regarding the co-ordination of the investigation and decisions as well as notification of any regulatory authorities. |  |  |  |
| 25.03 | Make available relevant information relating to recall or field alert activities within two (2) business days of the request to assist in investigations relating to product recalls. |  |  |  |
| 25.04 | CUSTOMER is responsible for the final decision and the coordination of any recalls or field alert activities related to finished drug product, with prior notice to SUPPLIER, whereas SUPPLIER shall not be prohibited hereunder from taking any action that is deemed necessary based on science and risk or that is required to be taken by applicable law. |  |  |  |
| 25.05 | Notifying regulatory authorities, external customers, consumers, or other relevant organizations or parties |  |  |  |
| 25.06 | Storing or disposing of affected/returned product |  |  |  |
| 25.07 | CUSTOMER shall notify SUPPLIER of any drug product recalls relating to the PRODUCT. |  |  |  |

**Issued by CUSTOMER**

First name, last name: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Function:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Date:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Signature: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Filled by SUPPLIER**

First name, last name: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Function:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Date:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Signature: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Appendix 03 to QA-YYYY-000: CUSTOMER and SUPPLIER contacts**

The following persons are responsible for answering quality relevant questions:

Grau Pharma GmbH (Jordangasse 7/12, 1010 Vienna, Austria)

|  |  |  |
| --- | --- | --- |
| **Name** | **Function** | **Contact** |
|  |  | Tel:  E-Mail: |

***“Short name” (Address, Town, Country)***

|  |  |  |
| --- | --- | --- |
| **Name** | **Function** | **Contact** |
|  |  | Tel:  E-Mail: |

**Confirmation of information:**

**CUSTOMER**

First name, last name: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Function:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Date:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Signature: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**SUPPLIER**

First name, last name: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Function:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Date:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Signature: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_