Agreement
on Tasks and the Division of Pharmaceutical Responsibilities in Contract Manufacturing and Testing

between

company address: CG

- hereinafter referred to as Contract Giver (CG) -

and

company address: CA

- hereinafter referred to as Contract Acceptor (CA) -

§ 1 Basis for the Agreement

1. This Agreement is valid to the manufacture of medicinal products. It is therefore in the sole responsibility of CG that the Products to be manufactured by CA are fulfilling the regulations for medicinal products (according to the European Good Manufacturing Practice (EU- GMP) and the regulations of the Ministery of Health for each country where applicable.
   In case the Products covered by this Agreement are not be understood as medicinal products regarding the local requirements, then it is in the sole responsibility of CG that the Products to be manufactured by CA are fulfilling all pertinent legal requirements or particular approval requirements.

2. CG is a pharmaceutical entrepreneur as per national drug law. CA is a drug manufacturer under national drug law only within the scope of the particular order issued by CG to CA.

3. CA holds a Manufacturer's Authorization under national drug law for the Products covered by this Agreement and is subject to monitoring by the competent authority. CA must inform CG without delay of any change to the Manufacturer's Authorization for the Products covered by this Agreement.

4. If not otherwise specified in this Agreement, the recognized pharmaceutical rules and the relevant statutory provisions prevailing in the purview of CA's legislation as well as the valid EU-GMP directives shall be applicable.

5. CA is to undertake toward CG the responsibility for complying with the rules of the „EU-guidelines for a Good Manufacturing Practice for Medicinal Products" to the extent as agreed in the division of tasks and responsibilities in this Agreement and its appendices.

6. CG is to make available to CA all necessary excerpts from the registration documents in general of the Common Technical Document (CTD) which are required for a proper manufacturing and testing. In particular, CG is to inform CA on any specific precautionary measures and protective measures and CG must inform CA immediately on any relevant change in the drug registration documents. CG is also responsible to supply CA with all necessary data covering the HSE (Health Safety Environment) aspects of manufacturing such as but not limited to the MSDS (Material Safety Data Sheet) of components. If CG wishes special provisions or guidelines that are not (yet) generally known or recognized to be followed for individual Products covered by the Agreement, CG must expressly inform CA of that fact in writing.

7. CA and CG are to designate as contacts for all technical pharmaceutical matters the persons named in Appendix 1. This appendix also contains the names of CA's key personnel responsible according to the EU GMPs and local requirements.
   Written notice of any changes and alterations of the contacts and persons responsible must be given in good time, upon start of their activities in the sense of this Agreement.

8. On CG's request, based on a justified interest, CA is to allow persons appointed by CG resp. their representatives and on the representative of the competent authorities, if necessary, to perform all inspections of the production and control facilities and to have access to all relevant data and documents.

9. CG declares to have the required permission of the supreme federal authority or the respective national authority for the marketing of the Products covered by this Agreement and that the CA site is duly registered into their Marketing Authorisation File.

§ 2 Object of the Agreement

CA shall manufacture for CG the Products itemized in Appendix 2. The division of pharmaceutical responsibilities shall be specified separately, for each Product of this Agreement, in Appendix 3 of this Agreement.

§ 3 Starting materials, semi-finished materials, bulk materials and packaging materials

1. CA shall be responsible for the proper quality of the starting materials purchased by CA and used for the manufacturing of the Products covered by this Agreement as well as for the primary and secondary packaging materials (packaging materials) purchased by CA. They shall be inspected by CA for quality and identity and released in accordance with the specifications agreed with CG.
   For the quality testing, certificates of analysis or test certificates of the respective manufacturers may be used.

2. Starting materials, packaging materials, semi-finished materials and bulk materials provided by CG are considered to be of the requisite quality, which is to be proved by a test certificate or release certificate. This release certificate has to be supplied automatically and without special request together with the delivery of the material. Otherwise, the material shall be considered as not having been released and shall be kept in quarantine. CA shall only check that the containers, closures and seals are intact and that the labelling of the containers is consistent with the delivery note.
   In case CA is responsible for final release of the finished Product for the market additional documentation may be required for proof of GMP-conformance of starting materials and has to be provided by CG.
   CA will not of his own volition make any additional quality check apart from a check of identity, unless such additional tests have been agreed in writing between CA and CG.

Kommentar: Bei beigestellten Ausgangsstoffen und Packmitteln, bei denen auf eine Qualitätsprüfung beim CA verzichtet werden soll, ist sicherzustellen, dass der beistellende Partner durch eigene Qualitätsprüfung deren Eignung überprüft hat. Die Materialien sind durch eine qualifizierte Person (in der Regel Leiter der QC) des Beistellenden freizugegeben.

3. CG shall be responsible for the constant quality of the starting materials, packaging materials, semi-finished materials and bulk materials which he provides.

4. Starting materials supplied by CG and in CA´s power of disposition remain the property of CG. The legal regulations regarding the acquisition or loss of property due to processing, compounding, mixing etc. of the material shall remain untouched.

5. The suppliers of starting materials, packaging materials, semi-finished materials and bulk materials shall be agreed upon between CG and CA and listed in Appendix 4 „Agreed suppliers of starting materials and primary packaging materials".

6. The division of pharmaceutical responsibilities for the starting materials and packaging materials shall be specified for each Product in Appendix 3 „Division of pharmaceutical/technical responsibilities".

7. The packaging materials which get in direct contact with the Product manufactured by CA (primary packaging materials) shall be only such material for which CA holds a safety certificate/ MSDS and described in the Marketing Authorisation File.

§ 4 Master manual, manufacturing instructions and manufacturing records

1. CA is to manufacture in accordance with the Marketing Authorization File. CG is to supply CA with the relevant parts of the Marketing Authorization File and to inform CA on any amendments immediately and without being asked.

Kommentar: „Relevant parts" soll hier die Information über die Herstellprozesse von Bulk- und bedeuten, z.B. Sektion 3.2.P-Arzneimittel

2. On the basis of these documents that are in compliance with the Marketing Authorisation File, CA is to create a manufacturing instruction, if necessary in cooperation with CG. CA shall hand to CG the manufacturing instruction to get CG's written approval.
   The responsibility for all product characteristics attributable to the manufacturing instruction shall be with CG.

Kommentar:Hinweis bei Marktfreigabe durch CA (§16 Abs. 2 Nr. 4 AMWHV): Die QP muss sicherstellen, dass der CG über ein funktionierendes Dokumentenmanagement und CC-Verfahren verfügt.

3. If amendments become necessary, the manufacturing instruction shall be replaced by a new amended version according to the procedure described under (2) above. With the approval of the amended version, the former version shall become invalid.

4. The manufacturing procedure is to be validated, and, when applicable (e.g. after changes of manufacturing process), be re-validated. CA and CG shall work together on the validation strategy, see appendix 3.

5. During the manufacturing process, CA is to carry out all in-process controls as described in the manufacturing instruction resp. testing instruction, to record them and to confirm the performance and conformity with the specification in the respective documentation.

6. CA has to create a Manufacturing and Testing Record on every production batch. The records must meet the requirements of the EU-GMP guidelines and the current Marketing Authorisation File of the Product and must contain the following information:
   - Name and dosage form, packaging size and kind of presentation
   - Date of manufacture and batch number,
   - Data on the amounts of the Product
   - Results of the in-process controls,
   - Certificate of Conformance (CoC),
   - Certificate of Analysis (CoA),
   - Deviations and OOS results,
   - Data of batch samples.

7. It shall be considered to be sufficient if other documents are referred to in the manufacturing report with regard to individual data.

8. The batch sizes are to be agreed upon between CA and CG and have to be in compliance with the Marketing Authorisation File

9. CG shall be responsible for the conformity of wording of labels and leaflets with the Marketing Authorization File.
   The Qualified Person has to verify that the correct labels and leaflets have been used.

Kommentar: Zulassungskonformität der Kennzeichnung fällt in die Verantwortung des CG (in D Informationsbeauftragter gem. § 74a AMG) und der freigebenden QP gem. § 16 Abs. 2 Nr. 4 AMWHV. Bei Freigabe durch CA ist die Verantwortung der QP zu beachten.

§ 5 Quality control and testing records

1. CA is to carry out the tests in accordance with the Marketing Authorization File. CG is to supply CA with the relevant parts of the Marketing Authorization File and to inform CA on any amendments immediately and without being asked.

Kommentar: „Relevant parts"soll hier die Information über die Prüfmethoden und Spezifikationenbedeuten, z.B. Sektion 3.2.S-Wirkstoffe

2. On the basis of the testing instructions that are in compliance with the Marketing Authorisation File, CA has to create internal testing instructions, if necessary in cooperation with CG. CA shall hand to CG the testing instructions to get CG's written approval.
   The responsibility for the suitability of all testing instructions and specifications shall be with CG.

Kommentar: Hinweis bei Marktfreigabe durch CA (§16 Abs. 2 Nr. 4 AMWHV): Die QP muss sicherstellen, dass der CG über ein funktionierendes Dokumentenmanagement und CC-Verfahren verfügt.

3. If amendments become necessary, the testing instructions shall be replaced by a new amended version according to the procedure described under (2) above. With the approval of the amended version, the former version shall become invalid.

4. The resulting testing procedures are to be validated resp. transferred to CA's laboratory, and, when applicable (e.g. after changes of testing instructions), be re-validated. CA and CG shall work together on the validation strategy.

5. CA is to carry out all controls as described in the testing instruction, to record them in a testing record and to confirm the performance and conformity with the specifications in the respective documentation. All records have to comply with the requirements of the GMP-guidelines.

§ 6 Miscellaneous

1. Change Control

CG and CA undertake to notifiy the other party in writing of any change which may have an impact on Product quality and / or the Marketing Authorisation File. Any such change may only be implemented when both parties give their consent in writing.

2. Deviations

CA shall be responsible for investigating and documenting according to CA's deviation management (SOP) all quality related deviations arising during manufacturing and testing. All deviations must be properly dealt with the latest at the time of issuing the Certificate of Conformance (CoC).

3. Out of Specification (OOS)

CA has to implement an OOS procedure (SOP). This has to be applied for any Out of Specification result on any work in progress (starting materials, bulk product, and finished product). CA assesses and approves corrective and/or preventive actions and will inform CG about confirmed OOS results.

4. Reprocessing / Reworking

Reprocessing and reworking shall be performed only exceptionally and be in conformance with the validated manufacturing processes and has to be agreed upon in writing by both parties.
In any case, product specification and product quality must not be affected.

Kommentar: Reprocessing (Umarbeitung) soll beschränkt sein auf die Aussagen des Kapitels 5.62 EU-GMP

5. Product Quality Review (PQR)

A Product Quality Review has to be performed on a regular basis according to the EC-GMP Guide. Details are specified in appendix 3. CG and CA will agree upon review periods and reporting times.

6. Ongoing Stability

Ongoing Stability Testing has to be performed on a regular basis according to the EC-GMP Guide. Details are specified in appendix 3.
CG and CA will decide together on the necessity of stability storage of additional batches in case of deviations or changes of the manufacturing or packaging process.
CA resp. CG shall inform the QP responsible for market release on the results of the on-going stability study in agreed intervals. Any OOS and OOT observed during on-going stability studies have to be reported to the responsible QP in due time.

§ 7 Documentation and reference and retained samples

1. CG and CA agree on the responsibility to store the documents of each manufactured Product as well as reference samples of the starting materials as well as reference and retained samples of the Product for its own purposes in a quantity sufficient for two full analyses (see annex 3).
   In case samples and documents are stored at CA they will be transferred to CG in case of business break-down.

Kommentar: Gemäß AMWHV muss die Herstell- und Prüfdokumentation beim Hersteller in den von der Herstellungserlaubnis umfassten Räumlichkeiten vorgehalten werden.

2. Together with the shipment, CG shall receive for each Product the documentation as agreed in Appendix 3 of this Agreement „Division of the pharmaceutical/technical responsibilities". CA is obliged to submit to the supervising authorities upon request the original documentation.

§ 8 Storage and shipment

1. The starting materials and the manufactured Products shall be stored by CA. CG is to inform CA in due time in writing on any storage risks resp. particular storage instructions in order to avoid damages. CG shall be liable for any damages and consequential damages attributable to insufficient information from CG.
   CG has to provide all the storage condtions regarding the Product to CA.

2. Shipment of the Products shall only take place if the release for shipment has been given by CA's Qualified Person.

3. Shipment under quarantine shall only be allowed in *exceptionnel cases* to be agreed between CA and CG and if the Authorised Person of CG has given written approval.

Kommentar: Das Inverkehrbringen nicht freigegebener Arzneimittel verstößt grundsätzlich gegen § 17 AMWHV. Für den Fall einer nicht erfolgten Freigabe bzw. Sperrung sind Regelungen im Vertrag erforderlich, die sicherstellen und regeln, dass CG in diesem Fall die Ware vernichtet oder zurück gibt.

4. CA is to take care that the Products are stored under suitable and proper conditions until they are handed over to the shipping agent. CG shall be liable for any damages that occurred as a result of a delayed pickup of the Products. Any deviations occuring from stipulated conditions have to be agreed upon separately in writing.

5. The responsibility for shipment under suitable conditions of the Products from CA's site to CG is defined in appendix 3.

§ 9 Confidentiality

1. CA and CG undertake to keep each other's know-how strictly confidential; this shall also apply for a period of 5 years after the Agreement has ended. Neither party shall be entitled to use the know-how of the other disclosed to it under this Agreement during and after the end of the Agreement.

2. The obligation of confidentiality and of not making use of the information shall not apply if

   a) the obligation has been annulled explicitly and in writing by the other party, or

   b) the information was already known to the other party before its disclosure under the Agreement and the other party declares this fact immediately, or

   c) the information is or gets in the public domain through publication or by other means, or

   d) the information becomes known to one of the parties without originating directly or indirectly from the other contracting party.

§ 10 Force majeure

Force majeure as well as stoppages, energy crises or shortage of raw materials for which the parties cannot be held responsible, consequences of labour disputes, official decrees or similar obstacles shall suspend the commitments for the parties resulting from this Agreement to the extent and for the duration of the hindrance. If such a hindrance arises for one of the parties, this party shall inform the other one immediately about kind, extent and expected duration of the hindrance and shall take efforts to redress it.

§ 11 Contracting of third parties

If CA does not do the work covered by this Agreement himself but contracts third parties to do it, the prior written consent of CG is required in each case. Upon conclusion of this Contract CG agrees to the subcontractors mentioned in the CA's manufacturing licence. CA is responsible for the qualification of the third party.

Agreements that are reached between CA and third parties must contain the same contractual obligations as the Agreement between CG and CA.

§ 12 Complaints and Recalls

1. The CG and CA will inform one another immediately about any batch recalls and complaints in connection with the Products listed in Appendix 2 and/or their raw materials and/or their packaging materials.

Kommentar: Gem. § 18 Abs. 1 AMWHV ist die freigebende QP über alle Maßnahmen zu bekannt gewordenen Meldungen über Arzneimittelrisiken zu informieren (z.B. auch Erkenntnisse aus Ongoing Stab. (siehe auch w18). CG und CA sollten sich gegenseitig unterstützen.

2. CA will investigate all quality related product complaints in a timeley manner according to CA's SOP and provide to CG a written report.

3. CG is responsible for making all Product recall decisions. CA will fully cooperate with CG in providing any data requested to support a recall decision. Such data should be provided as a matter of urgency.

§ 13 Final provisions

1. This Agreement shall come into force and effect with the signature of the parties hereto. It shall be applicable to all orders the execution of which is started by CA after signature of this Agreement, independent from the fact whether the order has been placed before or wether the validity of this Agreement has ended at the time when the order is being handled further.

2. The Agreement shall be concluded for an indefinite period and may be terminated subject to six month´s notice at the end of a year. The right for an extraordinary termination due to important reason is not affected. The notice shall be made in writing.

3. After termination of this Agreement, CA shall immediately return to CG at CG's expenses all stocks of starting material which belong to CG. If CA has purchased starting material for the Products of CG, he shall pass them on to CG in return for the reimbursement of the order value of such material.

4. Amendments to and supplements of this Agreement and its appendices as well as of this particular clause shall be made in writing. No side agreements have been made, neither verbally nor in writing.

5. If individual provisions of this Agreement are not valid or the Agreement is found to have a loophole, the validity of the other provisions shall not be affected. The contracting parties undertake to replace nonvalid provision by a provision which serves the intended economic purpose closest in a legally permissible way; the same shall be valid for loopholes in the Agreement.

6. The appendices attached to this Agreement shall form an essential part of this Agreement.

7. The Agreement shall be subject to German law. Place of jurisdiction shall be the defendant's location. Place of fulfilment for all deliveries and services under this Agreement shall be XXX.

Special arrangements:

Place, date

(Signature CG)
(Name of company)

(Name)
Authorised Person

(Name)
Authorised Person

Place, date

(Signature CA)
(Name of company)

(Name)
Authorised Person

(Name)
Authorised Person

Kommentar: Geschäftsführer und Sachkundige Person sollten den Hauptvertrag genehmigen

Legend

The complete Contract Manufacturing Agreement is consisting of:

An Agreement on Tasks and the Division of Pharmaceutical Responsibilities in Contract Manufacturing and Testing and 4 appendices.

List of contents

Appendices

- Appendix 1 „Responsible contacts“
- Appendix 2 „Products of the Agreement“
- Appendix 3 „Division of the pharmaceutical/technical responsibilities“
- Appendix 4 „Agreed suppliers of starting materials and primary packaging materials“
- Appendix 5: “Glossar”

Change Control

Date of amendment	Content of amendment	Reason of amendment