

**ACTIVE PHARMACEUTICAL INGREDIENTS COMMITTEE (APIC)**

# Quality Agreement Guideline & Templates

**Version 01**

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## Disclaimer

*This document represents voluntary guidance for API manufacturers and their customers, and the contents should not be interpreted as regulatory requirements. Alternative approaches than those described here may be used.*

## Foreword

The CEFIC\* Sector Group APIC (the Active Pharmaceutical Ingredients Committee) was founded in 1992 as a direct consequence of the rapidly increasing European regulatory requirements affecting the manufacture of Active Pharmaceutical Ingredients (APIs).

APIC represents producers of APIs and API intermediates in Europe. Its membership consists of more than 60 companies, located all over Europe, and of several national industry associations. For around 2/3 of its members, selling APIs and intermediates is their major business while ca. 1/3 of the members are primarily marketing final medicinal products.

APIC's focus is on worldwide Quality, Good Manufacturing Practice (GMP) and Regulatory matters relating to APIs and intermediates. Through the years APIC has developed into a high-profile industry association with an excellent, worldwide reputation.

APIC has already developed a series of guidance documents and position papers (see <http://apic.cefic.org/>). This document offers best industry practice and guidance in the establishment of a Quality Agreement between an API manufacturer and its customer. The guideline highlights the factors to consider when concluding such an agreement between both parties.

If you have any comments or suggestions for further improvement please contact the APIC Secretary at:

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*\* CEFIC (the European Chemical Industry Council): The Brussels-based organisation that represents the European Chemical Industry*

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## 2. Introduction

One of the biggest issues facing the pharmaceutical industry and patients today is quality, integrity and security of the pharmaceutical supply chain, preventing contamination (adulteration) and eliminating counterfeits. Quality Systems, Supplier Quality Management and Supply Chain Integrity have come into focus in the recent past. A suitable **Supplier Qualification Program** has hence to be implemented by each user of purchased APIs (or intermediates). A major element of such a supplier qualification program is the **Quality Agreement** between the manufacturer of the API/intermediate and the buyer or user of the API/intermediate. It increases transparency and traceability by improving the supply relationship between all parties involved in the manufacturing and distribution of APIs and intermediates.

### 2.1 What is a Quality Agreement?

A Quality Agreement under the scope of this guideline is a legally binding agreement that is mutually negotiated and concluded between (the Quality Departments of) API/intermediate manufacturers and their customers. It is intended to define, in a formalised manner, responsibilities relative to quality tasks to assure the manufacture and supply of safe materials (APIs or intermediates) acceptable for pharmaceutical use. A Quality Agreement is based on the quality procedures in place at both the API/intermediate manufacturer and its customer. The Quality Agreement also includes commitments between the parties regarding (a) the provision of information, documents, or samples, and (b) communication and notification rules including contacts. It creates mutual understanding of the quality & regulatory requirements relevant for material supply and both the API/intermediate manufacturer's and customer's respective obligations related to quality. By clearly delineating responsibilities, costly product quality issues resulting from miscommunication can be reduced or eliminated.

A Quality Agreement is a major element of an API/intermediate user's supplier qualification program but, of course, it is not a substitute for the supplier qualification processes, including audits as necessary, and for understanding the supplier processes and capabilities. A Quality Agreement must not contain any commercial or liability related terms, which should exclusively be dealt with in a Supply Agreement.

### 2.2 Relation to Supply Agreements

Supply Agreements (also known as Commercial Agreements) document the legal and business relationship between API/intermediate manufacturers and their customers. Quality Agreements usually complement the Supply Agreements (if present). If and to the extent a Quality Agreement has been agreed upon, it is basically recommended to avoid quality provisions in Supply Agreements, whenever and to the extent possible, and rather to include a simple reference to the specific, complementary Quality Agreement. Items not directly related to Quality and regulatory compliance (e.g., Safety, Health & Environment items) should rather be included in the Supply Agreement. Nonetheless, one may frequently find combined agreements, often called "Technical Agreements", mixing Quality/GMP/Regulatory items with detailed product-specific ("technical") contents and

other topics. It is recommended to implement separate agreements because these are easier to maintain.

Quality and Legal review of Supply Agreements should assure quality provisions are aligned/included in the corresponding Quality Agreements. Since Supply and Quality Agreement are often not generated at the same time or reviewed by the same people it is a must to define which document governs in case of conflict (see section III.3 of the Quality Agreement structure given in chapter 5).

### 2.3 The Issue

Due to the increasing desire to have Quality Agreements in place, there has been a trend to use templates to get a large number of agreements in place quickly. Many companies, both users or buyers and manufacturers of APIs and intermediates, have developed their own Quality Agreement templates. Unfortunately, these individual templates have often been designed to cover multiple types of products (APIs, intermediates, pharmaceutical excipients, and even packaging components), or to be used for both the purchase of (generic) APIs and contract manufacturing of (exclusive) substances (final APIs or intermediates). As a consequence, there have been extensive discussions between companies, and **significant time and resources spent** during all the review loops. At the end the **complexity** on both sides has considerably increased due to the high degree of diversity of agreements to be maintained. It is a real challenge for all organisations to keep control over all the individual agreements and commitments made between the various parties (as regards, e.g., timelines, document provisions, notifications vs. prior approvals).

### 2.4 The Solution

The issues mentioned above could be resolved by the use of **standardised templates**. Since APIC is committed to improving the relationship between API/intermediate users or buyers and API/intermediate manufacturers, APIC has developed this Quality Agreement Guideline plus the corresponding templates. The APIC Task Force that did the work consisted of members from both specialised API/intermediate manufacturers and companies primarily making finished drug products. Hence APIC believes that the result represents best industry practice considering the needs and requirements of both parties that enter into such a Quality Agreement.

## 3. Purpose and Scope

### 3.1 Purpose

This document intends to provide expert guidance to the API/intermediate industry and its customers for the implementation and maintenance of appropriate Quality Agreements.

It is obvious that consistent standards for such agreements will provide the following **benefits** to the industry:

- Lower workload (by reduced drafting time)
- Faster implementation (by reduced review times)
- Less complexity (by reduced diversity)

Following this document will provide the current “state of the art” for Quality Agreements in the pharmaceutical (API/intermediate) supply chain.

The APIC Quality Agreement Guideline and corresponding templates are designed to be a flexible model for preparing Quality Agreements wherever such an agreement is desired. It defines the appropriate items that should be addressed in a Quality Agreement. The template is designed to be global in scope and contents, thus being suitable for the use in all regions.

### 3.2 Scope

The guideline and templates cover agreements between the API/intermediate manufacturer and its customers (whether users or distributors). It does not cover agreements between distributors and their customers. Also not covered are the purchase of chemical/non-GMP raw materials by the API/intermediate manufacturer and out-contracted analytical services: the templates are not really suitable for these purposes but some parts of the templates may be used to compile an agreement for these areas.

There is both a template for “*generic APIs*” and a template for “*exclusive substances*”.

- Template for “*generic APIs*”: Designed for use between the (original) manufacturer of a generic API and its customer, that can either be the end user or a distributor. The term “generic API” is used for all APIs that in principle can be obtained from multiple sources, or are manufactured and supplied to multiple customers, as opposed to APIs that are sold only by the originator company or its exclusive licensees. Such generic APIs are off-patent; they are usually described in pharmacopoeial monographs, and supplied based on standard specifications.
- Template for “*exclusive substances*”: Designed for the use between the (original) manufacturer of APIs or intermediates exclusively made for one customer under a toll manufacturing contract as to EU GMP Guide Part I, chapter 7 or ICH Q7, chapter 16 (“Contract Manufacturing”, also known as “Custom Synthesis”), including substances still under development or for use in clinical trials, respectively.

### **3.3 Why two different templates?**

For “generic” APIs there will generally be a lower service level provided by the API manufacturers, compared to the higher service level in the custom synthesis business.

The users or buyers of a “generic” API will, of course, be provided with all information/data/documentation necessary to fulfil their regulatory and legal obligations, and compliance with applicable cGMPs will be ensured. However, as examples, they would typically not receive (copies of) all documents (e.g., full PQR), or they would not be involved in approval processes (e.g., approval of validation reports) or investigations (OOS etc).

Furthermore, the template for exclusive substances is more comprehensive as this could be used for the supply of clinical trial materials or Atypical APIs where the ICH Q7 Guideline does not apply in full, respectively.

### 4. Legal Requirements

Although Quality Agreements have become a common tool in our business and are intensively demanded by the authorities to be implemented they are not described in broad in the international guidelines.

Written contracts/agreements defining the responsibilities and communication processes for quality-related activities of the involved parties are mandatory for “**contract manufacture**” (see EU GMP Guide Part I, chapter 7, and ICH Q7 Guideline, chapter 16) or “**outsourced activities**” (see ICH Q10 Guideline, chapter 2.7), respectively. In principle, it is the responsibility of the contract giver to request the closure of such a contract/agreement with its contract acceptor(s).

The situation is less clear as regards “**purchased (starting) materials**” (see EU GMP Guide Part I, chapter 5.26 or ICH Q10, chapter 2.7), in other words the purchase of “generic” APIs. It may be implied from the mentioned guidelines that there needs to be an agreement in place but it is not explicitly required and thus, there is still no legal requirement.

Although there is no binding regulation on European level, there seem to be some countries that force to have such an agreement. For instance, the UK MHRA’s “GMP expectations for APIs” [see Reference 4] require that a “Quality Agreement must be in place with the API manufacturer/supplier(s)”, and the French Code de la Santé Publique (article R5124-47) [see Reference 1] requires a written contract on the respective GMP obligations between the manufacturers of medicines and their raw material manufacturers. The MHRA paper also lists some specific items that should be included in a Quality Agreement: arrangements for change control, access to audit, agreed specification, and sub-contracting.

Due to difficulties facing drug product manufacturers in assuring GMP compliance of certain “**Atypical APIs**” MHRA has also issued guidance on this specific issue. In these “GMP expectations of Non Traditional APIs” it is –reasonably– required that “an agreement/contract between the starting material manufacturer and the dosage form manufacturer (...) should be in place” since the existing GMP legislation does not appropriately cover the manufacture of such substances.

In the United States, Quality Agreements are simply assumed but not necessarily a (legal) requirement of the Food and Drug Administration (FDA). Although FDA issues no guidelines specifically for Quality Agreements in the pharmaceutical industry, nor is issuing a final rule on the subject, expectations of having implemented Quality Agreements are now relatively common, particularly in the area of contract manufacture [*“Establish Quality Agreements with suppliers, including procedures for handling changes, equipment, contract manufacturers, and notification about errors, deviations and changes.”*; see Reference 2], and violations have been recorded.

The Japanese “Ministerial Ordinance on Standards for Quality Assurance for Drugs, Quasi-drugs, Cosmetics and Medical Devices” [see Reference 9] requires in Article 7 that the Marketing Authorisation Holders of drugs should conclude a contract with their manufacturers (mentioned in the MA dossier) “*to ensure that the manufacturing control and quality control are conducted properly and efficiently by the manufacturers*”. Typically, for these GQP (Good Quality Practice) Agreements a specific template is used that significantly differs from the APIC templates.

## 5. Format and Structure of a Quality Agreement

### 5.1 General Aspects

The introduction and general provisions sections address the scope and terms and conditions of the agreement. The compliance section addresses the main quality and regulatory points and responsibilities that should be included in an appropriate Quality Agreement. The templates attached to this APIC guideline represent the compliance section (see typical structure of an agreement given further below).

The templates do, however, not mention every item of the pharmaceutical quality system since quality requirements that are sufficiently covered by reference to the applicable quality/GMP standard (as stated in section 1 of both templates) do not need to be reiterated in the agreement.

The annex to both templates (“division of responsibilities”) lists quality responsibilities that may require action by one or both parties. In order to allow a convenient and quick overview a tabular format has been chosen for the annex.

The format of the templates is intended to be flexible with the templates offering all the single elements needed for the compliance section of most Quality Agreements.

There are different possibilities how both parties may benefit from the use of a standardised template:

- The template may **completely replace** an own agreement
- The template may be **used as a basis** for a (slightly) modified, customised draft agreement
- **Certain sections** of the template may be used when drafting an own agreement
- The templates’ wording may be **used to resolve dispute** if mutually understood as good industry practice

Hence the templates constitute the ideal common starting point for any further negotiations on a Quality Agreement.

Modifying the templates should, however, be done with care and only as necessary to avoid lengthy negotiations. It is suggested that the generic API manufacturer prepares in advance a Quality Agreement based on the APIC guideline to begin the negotiation process with its customer when a Quality Agreement is requested. In the custom synthesis business the process will typically run the other way round.

Where necessary or requested by either party, country-specific or product-specific requirements may be added to the standard text.

It would significantly facilitate the discussion if any such alterations are clearly indicated by the drafting party to the other party (e.g., by coloured text) as this will help to achieve one of the major aims of the APIC project – speedier agreements.

Timelines mentioned in a Quality Agreement may be given in a descriptive way (most common terms: immediately, promptly, without undue delay, in a timely manner, within a reasonable period of time) or by a precise figure. Widely accepted definitions of the descriptive terms can be found in the glossary of this document. Time differences between the regions involved should be considered.

## 5.2 Standard Structure

The following sections should normally be included in all Quality Agreements:

### **I. Introduction/Purpose/Scope**

#### **I.1 Parties to the agreement**

*Note: although the APIC templates are intended for Quality Agreements between API/intermediate “manufacturers” (but not “traders” or “distributors”; see chapter 3.2) and their customers, the more general term “SUPPLIER” is used in the templates instead of “MANUFACTURER”. The reason is that even if you buy an API or intermediate from the original manufacturer you may be invoiced by another legal entity or the Supply Agreement is concluded with another legal entity of the same company, especially if the manufacturing site is part of a bigger company (also see next note).*

Example wording:

This Quality Agreement is by and between <full supplier name> located at <full supplier address>, hereafter referred to as SUPPLIER and <full customer name> located at <full customer address>, hereafter referred to as CUSTOMER. Whereas, SUPPLIER supplies APIs suitable for pharmaceutical use to CUSTOMER.

*Note: In case the party that supplies the API(s) or intermediate(s) is a different legal entity within the same company, or the manufacturing sites involved in the manufacture of the API(s) or intermediate(s) are different legal entities of the same company, the following additional wording would be appropriate:*

SUPPLIER sells and markets products produced by itself or its Affiliates, inter alia <full affiliate(s) name> located at <full affiliate(s) address>, which Affiliates have the ability and desire to, as sub-contractors, manufacture and SUPPLIER has the desire to supply the products. SUPPLIER is responsible for the trade and sample packaging of the released products. Each reference to SUPPLIER shall in the following hence be interpreted as a reference to SUPPLIER and/or the manufacturing entity, as applicable.

*Note: The following definition of “Affiliate” may be added to the preceding paragraph or listed in the Definitions section (I.4).*

For the purposes of this Quality Agreement, the term “Affiliate” shall mean any company controlling, controlled by or under common control with the respective party. The term “control” shall mean the possession, directly or indirectly, of more than 50 % of the respective shares or the power to direct the management or policies of such company or party.

#### **I.2 Products covered by the agreement**

Example wording:

This Quality Agreement pertains to the following product(s), hereafter referred to as SUBSTANCE(s): <list or see attachment>.

## I.3 Site(s) involved

*Note: Sites at which SUBSTANCE(s) are produced should be mutually agreed upon. The SUPPLIER sites involved can be specified here if needed (or may refer to an appendix). If the sites involved are not listed in this agreement, it should be indicated where the agreed sites are specified. The sites can also be sites of affiliates of the SUPPLIER (see also I.1).*

## I.4 Definitions and abbreviations (optional)

Example wording:

Capitalised terms used but not otherwise defined in this Quality Agreement will have the meanings ascribed thereto in the Supply Agreement, as applicable. Unless this Quality Agreement will expressly provide to the contrary, the following terms used herein, whether used in the singular or plural, will have the respective meanings set forth below:

<List definitions/abbreviations>

## II. Compliance Section

The appropriate Quality Agreement template (generic or exclusive) is inserted here (see Appendices A and B to this guideline).

Use instructions for the Quality Agreement templates:

**Text highlighted in yellow** indicates alternative or optional wordings.

*Notes in grey boxes* are for information/explanation purposes only, and they would not appear in the actual Quality Agreement.

**Text in green boxes** (template for exclusive substances only) represents specific conditions for substances still under development.

## III. General Provisions

*Note: The general provisions mentioned hereunder are required for a stand-alone Quality Agreement, however, in case the Quality Agreement is part of or appendix to a Supply Agreement they would usually be included in the Supply Agreement and do not need to be repeated in the Quality Agreement.*

### III.1 Term of agreement

Example wording:

This Quality Agreement shall become effective and binding upon the date of the final signature and shall remain in effect until 2 years after the last delivery of SUBSTANCE by SUPPLIER to CUSTOMER unless the Parties specifically agree in writing an extension of the Quality Agreement. Either Party may terminate this Quality Agreement by giving 6 months written notice to the other Party.

*Note: In case the effective date is not determined by the final signature, the effective date should be given elsewhere in the Quality Agreement.*

### **III.2 Assignment**

Example wording:

Neither Party shall have the right to assign any or all of its rights or obligations under this Quality Agreement without the other Party's prior written consent, which consent shall not unreasonably be withheld. The foregoing notwithstanding, prior written consent shall not be required (i) in case of an assignment of rights or obligations to an Affiliate of the assignor (optional extension: provided that the assignor procures that any such Affiliate assigns such rights back to the assignor immediately before ceasing to be an Affiliate of the assignor), or (ii) in connection with a merger, consolidation, or a sale of all or substantially all of party's assets to a third Party, except if such merger, consolidation or sale is with a competitor of the other Party.

### **III.3 Related agreements**

Example wording:

If a supply agreement is in place between SUPPLIER and CUSTOMER, and there are any inconsistencies between the supply agreement and the Quality Agreement, the supply agreement will take precedence over the Quality Agreement in all non-quality related matters unless otherwise stated in the supply agreement. The Quality Agreement will take precedence in all quality related matters.

### **III.4 Confidentiality (optional)**

*Note: It is recommended to refer to separate documents pertaining to confidentiality, e.g. confidentiality agreement (also referred to as a confidential disclosure agreement) but may be defined here according to SUPPLIER's policy.*

### **III.5 Choice of Law (optional)**

*Note: A choice of law should always be specified in a supply agreement. If a reference shall also be included in the Quality Agreement the following wording is recommended:*

*"The Parties agree that this Quality Agreement shall be governed by and construed in accordance with the law applicable to the supply agreement between the Parties or their Affiliates pertaining to the SUBSTANCE(s)."*

*Typically the law of the country where the SUPPLIER is located is chosen. For instance, in Europe (except Denmark and the UK), the new EU Regulation No. 593/2008 - "Rome I" - will apply as of December 17, 2009, and as most of the jurisdictions it declares that the law of the country where the party required to effect the characteristic performance of the contract has its habitual place of residence shall govern the contract.*

### **III.6 Survival Clause (optional; for exclusive substances)**

Example wording:

The <list particular provisions> shall survive <give number> years from expiration or termination of this Quality Agreement.

*Note: This clause relates to provisions that by their sense or context are intended to be continued beyond termination of the Quality Agreement, for instance the right to audit, maintenance of lot traceability, responses to complaints or authority requests, ongoing stability studies, or document/record/sample retention. This clause is more common in the custom synthesis business.*

### **IV. Signatories**

### **V. Quality Contacts**

*Note: List the relevant contact persons (name, position, phone number, e-mail) from each party that will be responsible for communications related to this Quality Agreement. This information can be provided in an attachment.*

### **VI. List of Appendices**

Examples of documents typically attached to a Quality Agreement (list not exhaustive): product specification(s), example CoA(s), list of sub-contractors, example label, and description of the packaging.

## 6. Quality Agreement Review and Maintenance

### 6.1 Negotiation, Review and Approvals

The negotiation and review of a Quality Agreement should always be a collaborative effort of different departments of the parties involved: Quality representatives negotiate and review the quality sections, and Legal representatives negotiate and review the legal provisions. Other departments (e.g., Purchasing, Marketing) may be involved, as appropriate. It is recommended that in the negotiation phase a sole functional unit, preferably the Quality Unit, acts as the voice of the entire company.

The Quality representatives at API/intermediate manufacturer and customer must assure that the quality provisions can be met, i.e., that the obligations of the agreement are consistent with the quality systems established at the respective sites [*Note: this is very important in case multiple sites or affiliates at either party are affected by the agreement*], and both parties must understand the impact of the agreement provisions on patient safety and product quality.

In order to allow review of any modified wording or any requirements added during the negotiation phase and to ensure transparency and traceability the “track changes mode” should be used. A “cleaned” version would be created only directly before signature, after all parties are satisfied with the draft agreement.

Clarity of language in the Quality Agreement is essential. Quality Agreements have no room for ambiguity. It is generally recommended that the wording of Quality Agreements is kept “simple” or “non-legal” (at least all sections except the general provisions (see chapter 5.2, section III of this document) since it is primarily written for Quality people, and these people have to understand and follow the provisions.

A Legal review of the final draft agreement is a “must”, irrespective if the Quality Agreement is a stand-alone document or if the Supply Agreement is negotiated at the same time. Not having the Quality Agreement undergo a qualified review by Legal department may expose the company to potential liability. It is, however, not the Legal representatives’ task to interpret GMPs and change the language unless potential liability exists. It is their job to look at the document from the point of view of someone who is providing a level of protection to the company.

The following wording recommendations aim to avoid future dispute and unexpected liability with respect to requirements and commitments in Quality Agreements, and they have been considered in the APIC templates:

- Do not use expressions such as “SUPPLIER guarantees”, “SUPPLIER represents and warrants”, or “SUPPLIER ensures”, in Quality Agreements. “Guarantee”, in particular, triggers extended rights of the purchaser, liability without any fault, and leads to extended statute of limitations.
- Instead use “neutral” expressions like “SUPPLIER shall“, “SUPPLIER undertakes”, or “SUPPLIER shall make reasonable endeavours” (but not “best” endeavours).

When a supply agreement exists, or is being generated at the same time as the Quality Agreement, the reviewers should assure that any quality provisions captured in the supply agreement are also reflected and/or not contradicted in the Quality Agreement.

Since all Quality Agreements require legally binding signatures, it is the responsibility of each party to assure the signatures in the Quality Agreement reflect the legally binding

signatures representing each party. Depending on the signing rules in each company two or even more signatures might be required. At least one signature should come from an authorised Quality representative.

### **6.2 Maintaining Agreements**

Any Quality Agreement should be readily available to all persons or units with obligations stipulated in the agreement. It is recommended to have a system in place for tracking commitments originating from the various Quality Agreements.

Once approved all Quality Agreements must be kept current by both parties during the entire effective period. An amendment/addendum process should allow for simple updating, e.g., for contact or specification updates. Any amendment/addendum should be maintained with the original agreement.

Basically, there are different options to define the review frequency for an established Quality Agreement: periodic review (e.g., during the compilation of the annual PQRs) or frequency based on risk. A combination of both options might be the best solution, namely a 3-years review period in the absence of serious quality incidents.

### 7. References

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### 8. Appendices

- Appendix A: Quality Agreement Template for generic APIs
- Appendix B: Quality Agreement Template for exclusive Substances

## 9. Glossary

**Active Pharmaceutical Ingredient (API)** - Any substance or mixture of substances, intended to be used in the manufacture of a drug (or: medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease 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 product or process which is outside the normal process capability or which indicates a reasonable probability that the product will fail to comply with specification before the end of its assigned shelf-life or retest period.

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

**(Governmental) 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 Agency for the Evaluation of Medicinal Products (EMA).

**Business day** – Any day of the week, other than Saturday, Sunday, or day on which the party 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 which demonstrates that the Product complies with the requirements of 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 which provides 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 which provides 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, cGMP, and the relevant pharmacopoeial monographs, as applicable.

**Contract** – Business agreement for supply of goods or performance of work at a specified price.

**Contract Manufacture** – 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, or a predefined critical parameter, or an unanticipated event that could have an adverse impact, respectively, on the final SUBSTANCE quality and/or stability and/or physical characteristics.

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**Customer** – The company or organisation receiving the product (API or intermediate) once it has left the control of the supplier; includes users and distributors.

**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 product (usually an API) used in the manufacturing, processing, packaging, and storing of one or more drug (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 premises of the manufacturer to the end user, or to an intermediate point by means of various 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) is the applicable term in the United States. For the purposes of this guideline, 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, cGMPs, NDA regulations, and other relevant provisions enforced by any applicable governmental authority), ordinances and other pronouncements having the binding effect of law of any governmental authority.

**Manufacturing License** – With respect to a country, any regulatory authorisation required to manufacture one or more products or classes of product as granted by the relevant governmental authority.

**Non-conformance** – Departure of a quality characteristic from its intended level or state such as to cause an associated material or activity not to comply with its specification, cGMP, marketing authorisation or applicable law.

**OOE** – Out-of-expectation. A value obtained that still meets the set requirements but is significantly different from the previous values or former trend

**Original Manufacturer** – Person or company manufacturing a material to the stage at which it is designated as a pharmaceutical starting material.

**Product Quality Review** – 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 that is mutually negotiated and concluded between (the Quality Departments of) API/intermediate manufacturers and their customers. It is intended to define, in a formalised manner, responsibilities relative to quality tasks to assure the manufacture, supply and use of safe materials acceptable for

## APIC Quality Agreement Guideline

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pharmaceutical use. It may also include commitments between the parties regarding (a) the provision of information, documents, or samples, and (b) communication and notification rules including contacts.

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

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

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

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

**Site** – A location where the API or intermediate manufactured. This may be any operational area within the supplier’s facility referred to in the section “Parties to the agreement” of the Quality Agreement (see chapter 5.2, I.1 of this guideline), or at a remote facility that may be the facility of an affiliate of the supplier or a sub-contractor.

**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 original contract acceptor’s cGMP obligations under the License, Supply or Quality Agreements.

**Supplier** – Person or company providing APIs or intermediates on request. For the purpose of this guideline, a supplier is the (original) manufacturer or another legal entity of the same company that supplies the material. In general, suppliers may also be traders or distributors.

**Supply chain** – For the purpose of this guideline, supply chain is defined as all steps in the entire chain of distribution starting from the point at which an API or intermediate is transferred outside the control of the original manufacturer’s material management system downstream to the final user(s).

**Timely manner** – As soon as can be expected considering the typical operations and processes at manufacturers, the defined responsibilities and the agreed communication pathways. A “reasonable period of time” is considered as practically synonymous. The exact period of time depends on the respective subject.

**User** – A party who utilises an API in the manufacture of a drug product or an intermediate in the manufacture of an API.

**WHO** – World Health Organization

**Without undue delay** – Generally no more than five (5) business days. This period may be exceeded due to events or circumstances beyond the reasonable control of the responsible party.

*Note: For all other GMP-relevant terms it is referred to the glossary of the ICH Q7 Guideline.*

# Appendix A:

## Quality Agreement Template for Generic APIs

(Compliance Section only)

*Note 0.1: the term “**generic API**” is used in this template for all APIs that in principle can be obtained from multiple sources, or are manufactured and supplied to multiple customers, as opposed to APIs that are sold only by the originator company or its exclusive licensees. Such generic APIs are off-patent; they are usually described in pharmacopoeial monographs, and supplied based on standard specifications.*

### 1. Applicable GMP Standard

SUPPLIER shall manufacture the SUBSTANCE(s) listed in Appendix X in compliance with the ICH Q7 Guide.

### 2. Certificate of Analysis / Conformance (optional)

A Certificate of Analysis and a Certificate of Conformance (optional) are required for each batch of SUBSTANCE shipped to CUSTOMER.

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. The Certificate of Analysis states that the batch is suitable for release, and it must include – as a minimum –

- SUPPLIER name and address, incl. telephone number
- Name and address of original manufacturer, if SUPPLIER is not the original manufacturer
- SUBSTANCE 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 SUBSTANCE.

*Note 2.1: the date of manufacture is considered as optional.*

#### Optional:

The Certificate of Conformance states that the subject lot was produced in accordance to the applicable DMF, CEP or pharmacopoeial monograph(s), and in compliance with all applicable cGMP requirements.

Certificate of Analysis and Certificate of Conformance may be issued as separate documents or combined to a single document, as appropriate.

*Note 2.2: the Certificate of Analysis may be attached as an appendix; in any case it should match the SUBSTANCE specification.*

### 3. Change Control

SUPPLIER shall have a documented and effective change control system in place. SUPPLIER shall inform CUSTOMER of any significant changes to the manufacture of the SUBSTANCE, which may have an impact on the quality of supplied SUBSTANCE, and/or on any regulatory applications related to the SUBSTANCE. SUPPLIER shall notify CUSTOMER within a reasonable time, prior to implementation, to allow CUSTOMER to assess the potential impact of the change upon the SUBSTANCE supplied or its use by CUSTOMER.

The implementation of major changes (i.e., changes requiring authorities' pre-approval) shall not occur until the CUSTOMER has given written approval.

SUPPLIER shall only supply CUSTOMER with SUBSTANCE approved under any applicable DMF and/or CUSTOMER's existing regulatory filings until such time as the SUBSTANCE manufactured following such change is permitted under the regulatory filings therefore.

For those changes required to comply with applicable laws and regulatory agency requirements, SUPPLIER shall notify CUSTOMER of such requirements after SUPPLIER becomes aware of the need for such change.

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 acknowledgement of the validity of the notification and, depending on the type of change, the acceptance or approval of the change by the competent authorities.

### 4. Right to Audit

SUPPLIER shall allow ~~upon signature of a special confidentiality agreement~~ CUSTOMER or its representatives 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 the SUBSTANCE(s), including pertinent documentation. Any such audit shall take place during normal business hours and must not interfere with SUPPLIER's manufacturing operations.

The results of the audit and the observation(s) shall be sent to SUPPLIER by means of a written report. SUPPLIER must ensure a satisfactory follow up to the observations made during the audit performed by the CUSTOMER, and take corrective actions mutually agreed upon by the parties.

*Note 4.1: target timelines for both report and response may be added; a 4-weeks period is quite common, respectively.*

The audit frequency shall depend upon the results of the previous audit(s) and the quality performance of SUPPLIER. In the absence of critical quality incidents the frequency shall be not more than once every three (3) years.

### 5. Authority Inspections

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 cGMP inspections and impacting the quality of the SUBSTANCE intended to be shipped to CUSTOMER and/or potentially affecting the ability of SUPPLIER to produce or ship the SUBSTANCE.

### 6. Sub-contracting

SUPPLIER will use its established cGMP systems for evaluation, approval and maintenance of all sub-contracted services with a cGMP impact on SUBSTANCE manufactured. SUPPLIER shall notify CUSTOMER of any existing or new sub-contractor used for any cGMP-relevant service if the regulatory filings of the SUBSTANCE are concerned.

### 7. Retention of samples (final SUBSTANCE)

*Note 7.1: one of the two conditions given below should be chosen, depending if an expiry date or a retest date has been defined for the SUBSTANCE.*

SUPPLIER will store SUBSTANCE 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 < one (1) year after the expiry date of the batch assigned by SUPPLIER or for three (3) years after distribution, which ever is the longer > or < for three (3) years after the batch is completely distributed by SUPPLIER >.

*Note 7.2: "specification analysis" means "analysis according to the agreed specification" that may be identical with "compendial analysis" (if specification is equivalent to current pharmacopoeial monograph), or different in case there is no pharmacopoeial monograph, or if the agreed specification exceeds the monograph.*

### 8. Retention of records/documentation

*Note 8.1: one of the two conditions given in 8.1 should be chosen, depending if an expiry date or a retest date has been defined for the SUBSTANCE.*

8.1 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 unauthorised access, for < one (1) year after the expiry date of the batch assigned by SUPPLIER or for three (3) years after distribution, which ever is the longer > or < for three (3) years after the batch is completely distributed by SUPPLIER >.

8.2 SUPPLIER will make the original records related to the manufacture of the SUBSTANCE available for CUSTOMER during an on-site audit.

8.3 Validation documents should be archived for as long as SUBSTANCE is supplied or for 7 years after the version became obsolete.

*Note 8.2: a period of 7 years is recommended by the APIC "How to do" Document on the ICH Q7 guideline. A 10 years period is also often used.*

### 9. Stability

SUPPLIER has assigned retest dates (or expiry dates, where applicable), storage and shipping conditions, based upon stability studies.

SUPPLIER is responsible for performing on-going stability studies for the SUBSTANCE. At least one batch per year should be tested to ICH requirements (long-term storage conditions only).

*Note 9.1: in case the SUBSTANCE is not manufactured in a certain year the above requirement is not applicable.*

SUPPLIER is responsible for performing appropriate stability studies on the SUBSTANCE arising from process changes.

SUPPLIER will provide stability data to CUSTOMER upon reasonable request (e.g., if required according to the applied registration procedure).

*Note 9.2: Results of the on-going stability program are not routinely provided to customers.*

### 10. Complaints

SUPPLIER will respond to complaints by the CUSTOMER in a timely manner and according to formally agreed procedures.

SUPPLIER will inform CUSTOMER in a timely manner and in writing on the conclusions driven by the investigation performed and the corrective/preventive actions defined.

In case the investigation could not be finalized within 20 business days, SUPPLIER will provide an interim report to CUSTOMER.

*Note 10.1: target timelines for both initial and concluding responses may be added; for the concluding response a period of 20 business days is quite common.*

CUSTOMER will make relevant information and samples of the affected SUBSTANCE batch(es)/lot(s) available to assist in the investigation of SUPPLIER (as appropriate).

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 patients' health or safety).

The statutory and/or contractual obligations of CUSTOMER to inspect the goods upon delivery and to promptly notify any defect or shortage remain unaffected.

### 11. Recall

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 SUBSTANCE or finished drug product made thereof.

SUPPLIER and CUSTOMER consult and decide on roles and responsibilities regarding co-ordination of the investigation and decisions.

CUSTOMER is responsible for the final decision and the coordination of any recalls or field alert activities related to finished drug product, 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.

### 12. Product quality review

SUPPLIER shall allow CUSTOMER to review the annual Product Quality Review (PQR) for the SUBSTANCE(s) during an on-site audit.

### 13. Storage and distribution

*Notes:*

*13.1: Storage: special storage requirements for the SUBSTANCE(s) should be clear.*

*13.2: Distribution: either in the Supply Agreement or in the Quality Agreement the responsibilities for the whole supply chain should be defined; reference to GDP (IPEC, WHO) is recommended. The following text is written for a case where the SUPPLIER is responsible for the transportation from the manufacturing site to the CUSTOMER's receiving site (and needs to be changed, if responsibilities are different).*

SUPPLIER shall make commercially reasonable efforts to exclude, during packaging, storage, and shipping of the SUBSTANCE(s), the possibility of deterioration, contamination, or mix-ups with any other material.

SUPPLIER shall comply with the following requirements in relation to distribution of the SUBSTANCE(s):

- Distribution in accordance with storage conditions stated on the labels
- Contracts with hauliers and shipping agents
- Ability to recall SUBSTANCE from distribution network
- Quarantine SUBSTANCE with questionable quality
- Utilise tamper evident seals on all packaging
- SUPPLIER will qualify hauliers and shipping agents used to transport the SUBSTANCE(s).

SUPPLIER will provide an up-to-date MSDS to CUSTOMER with each shipment or at least on an annual basis.

This agreement does not absolve the SUPPLIER from complying with any legal requirements in relation to the transportation of the SUBSTANCE(s).

### 14. Undesirable contaminants

*Note 14.1: the three items listed below constitute the most frequently requested ones. Others may be added as appropriate.*

#### 14.1 BSE/TSE

SUPPLIER shall provide to CUSTOMER a BSE/TSE certificate for the SUBSTANCE(s) listed in accordance with the EMEA Note for Guidance EMEA/410/01 (current revision). The certificate shall indicate if the SUBSTANCE(s) is (are) of human or animal origin, and if materials of human or animal origin are used during the manufacturing process of the SUBSTANCE (s). An updated BSE/TSE certificate must be issued after any change to the manufacturing process which involves new raw materials or for raw materials that have been sourced from a different supplier.

### 14.2 Residual solvents

SUPPLIER shall provide to CUSTOMER a residual solvents statement for the SUBSTANCE(s) listed in accordance with the ICH Q3C guideline. An updated statement must be issued after changes to the manufacture of the SUBSTANCE(s), if applicable.

### 14.3 Metal catalyst/reagent residues

SUPPLIER shall provide to CUSTOMER a statement on metal residues for the SUBSTANCE(s) listed in accordance with the EMEA “*Guideline on the specification limits for residues of metal catalysts or metal reagents*” (EMEA/ CHMP/ SWP/ 4446/ 2000) and other applicable regulations. An updated statement must be issued after changes to the manufacture of the SUBSTANCE(s), 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.

## 15. HAPIs

15.1 SUPPLIER shall not conduct production and handling of highly sensitizing materials (such as penicillins or cephalosporins) in the equipment being used for the SUBSTANCE(s). Production of such materials in the same building being used for the SUBSTANCE(s) is permitted only if performed in a closed and dedicated system.

15.2 In case of highly active or toxic materials, such as potent hormones, cytotoxic compounds, or other potentially hazardous materials manufactured by the SUPPLIER in the same facilities as used for SUBSTANCE, validated inactivation and/or cleaning procedures should be in place.

## 16. Raw materials

N/A

## 17. Qualification / Validation

N/A

*Note 17.1: qualification and validation activities according ICH Q7, chapter 12; not necessary to give more details in the agreement.*

### 18. Reprocessing

N/A

*Note 18.1: not to be included in the agreement; reprocessing shall be performed according to the registration dossier and ICH Q7, chapter 14.2. No further information on reprocessing necessary as far as described in the DMF or CEP dossier (generic APIs). If ICH Q7 as well as the registered procedures are followed there is actually no justified reason to refuse the delivery of reprocessed batches of SUBSTANCE.*

### 19. Reworking

Reworking must be performed, if at all, according to the SUBSTANCE 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.

*Note 19.1: on agreement reworking might be prohibited.*

### 20. Deviations / OOS (incl. stability)

In case of serious quality incidents observed only after shipment of batches of the SUBSTANCE, SUPPLIER shall promptly and appropriately notify CUSTOMER thereof.

*Note 20.1: information on OOS results in stability is only necessary if there is an impact on the retest period or the storage condition or the packaging material (such information would be given through a change control procedure anyway; see also section 3).*

### 21. Packaging

In addition to the requirements in ICH Q7 the following shall apply to the packaging of the SUBSTANCE(s):

The specifications for packaging materials including tamper evident seals must be in accordance with the regulatory documentation related to the SUBSTANCE(s).

#### Optional:

SUPPLIER shall package the SUBSTANCE using the components, closures and tamper evident seals as specified in Appendix X.

*Note 21.1: the list in Appendix X may include both primary packaging materials and secondary ones, e.g. pallets, wrapping etc. There may be the need to define and explain any coding on the seals.*

< List other security measures here, as applicable. >

*Note 21.2: the following paragraph is only applicable in very specific cases.*

#### 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.

### 22. Labelling

N/A

*Notes:*

*22.1: the shipping label may include additional information (e.g., CUSTOMER material code); details may be defined in the Supply Agreement;*

*22.2: labelling should be described in sufficient detail if done on behalf of the CUSTOMER;*

*22.3: an example of the label may be provided in an appendix to the Quality Agreement.*

### 23. Regulatory documents

SUPPLIER is responsible for preparation, submission and maintaining the appropriate registration documents for the SUBSTANCE (i.e. dossier for CEP, DMF, or equivalent).

SUPPLIER is responsible for all regulatory contacts with the relevant regulatory authority with jurisdiction over the SUBSTANCE.

Upon written request, SUPPLIER will allow CUSTOMER to refer to SUPPLIER's registration documents for the SUBSTANCE, in order to support CUSTOMER's Marketing Authorisation Applications for finished drug product made from SUBSTANCE.

SUPPLIER will provide current information to CUSTOMER, as reasonably requested for the SUBSTANCE by guidance for submission of any regulatory dossier by CUSTOMER for finished drug product made from SUBSTANCE. Such information will include either access to CEP (including the appropriate stability data for the SUBSTANCE, if no retest date is defined in the CEP), or applicants part to DMF, or equivalent.

CUSTOMER is responsible for submitting the regulatory dossier for Marketing Authorisation Application associated with any finished drug products made from the SUBSTANCE. Such regulatory dossier, as it pertains to SUPPLIER, will refer to SUPPLIER's CEP, DMF or equivalent, where applicable.

**Optional: Appendix X will include the list of SUPPLIER's supportive registration documents that are available at the signature of this Quality Agreement.**

### 24. Product release

**Optional:**

**SUPPLIER will not ship any SUBSTANCE to CUSTOMER until the SUBSTANCE is released, unless prior written approval has been received from CUSTOMER to perform such a shipment under quarantine.**

### 25. Reference standards

All reference standards should be stored in accordance with the suppliers recommended storage conditions and used within their given expiry or retest date.

SUPPLIER shall provide to CUSTOMER reasonable quantities of any non-compendial, commercially not available reference standards necessary to perform the tests included in the SUBSTANCE specification.

### **26. Specifications**

Specifications for the SUBSTANCE(s) are detailed in Appendix X.

### **27. Analytical methods**

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).

Compendial analytical methods must be verified and all others must be validated prior to use.

## Annex: Division of Responsibilities

[ C = CUSTOMER; S = SUPPLIER ]

<b>A Regulatory Compliance</b>		<b>C</b>	<b>S</b>
1.	Adhere to approved registration documentation (Marketing Authorisation, NDA, IND, DMF, CEP, etc, as applicable)	X	X
2.	Maintaining valid manufacturing license(s), as applicable		X
3.	Maintaining site master file, as applicable		X
4.	Inform on significant changes		X
5.	Submitting change notifications/applications to authorities	X	
<b>B Purchasing, Manufacturing and Analytical Testing of API Starting Materials (SMs), Raw Materials, Process Aids, Intermediates, and SUBSTANCE</b>			
6.	Setting specifications for SUBSTANCE, materials and intermediates		X
7.	Purchasing materials according to specifications		X
8.	Qualifying and monitoring material suppliers		X
9.	Sampling and testing of incoming material, as appropriate		X
10.	Generating and approving Master Batch Procedure/Record		X
11.	Manufacturing SUBSTANCE according to Master Batch Procedure (incl reprocessing, packaging, labelling)		X
12.	Performing batch record review		X
13.	Assigning batch numbers		X
14.	Sampling, testing, and releasing of intermediates and SUBSTANCE		X
15.	Performing IPCs		X
16.	Storing retention samples		X
17.	Documenting all deviations, investigating OOS and critical deviations		X
18.	Maintaining (certified) reference standards		X
<b>C Purchasing and Testing of Packaging Material</b>			X
<b>D Labelling, Label Printing and Label Reconciliation</b>			X
<b>E Storage and Shipment</b>			
19.	Storing API under labelled conditions	X	X
20.	Maintaining storage conditions during transportation until agreed transition point		X

## APIC Quality Agreement Template (Generic APIs)

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<b>F Documentation</b>		<b>C</b>	<b>S</b>
21.	Establishing synthesis scheme (including definition of API SMs)		X
22.	Archiving the original manufacturing and control documents		X
23.	Issuing Certificate of Analysis / <b>Certificate of Conformance (optional)</b>		X
24.	Preparing reports on OOS, critical deviations		X
25.	Providing test procedures, quality statements, stability reports, and other documents as mutually agreed between the parties		X

<b>G Equipment Cleaning</b>			X

<b>H Qualification / Validation</b>			
26.	Qualifying of equipment, utilities and facilities		X
27.	Validating the manufacturing process, cleaning procedures, analytical methods, and computerised systems		X

<b>I Stability Program</b>			
28.	Performing stability studies, incl on-going stability studies, under ICH conditions (incl testing)		X
29.	Assigning retest period (or shelf-life)	X	X

<b>K Product Quality Review</b>			X

<b>L Complaints and Recall</b>			
30.	Investigating customer complaints related to SUBSTANCE		X
31.	Implementing corrective actions, if necessary		X
32.	Responding to customer(s)		X
33.	Deciding to initiate recall	X <sup>1)</sup>	X <sup>2)</sup>
34.	Notifying authorities, external customers, or consumers	X <sup>1)</sup>	X <sup>2)</sup>
35.	Clarifying root cause	X	X
36.	Storing or disposing returned product	X <sup>1)</sup>	X <sup>2)</sup>

<b>M Sub-Contracting</b>			
37.	Qualifying and monitoring sub-contractors		X

<sup>1)</sup> Responsibility regarding drug product made from SUBSTANCE

<sup>2)</sup> Responsibility regarding SUBSTANCE

## Appendix B:

# Quality Agreement Template for Exclusive Substances

(Compliance Section only)

**Scope: APIs or intermediates exclusively made for one customer under a toll manufacturing contract as to EU GMP Guide Part I, chapter 7 or ICH Q7, chapter 16 (“Contract Manufacturing”, also known as “Custom Synthesis”), including substances still under development resp. for use in clinical trials.**

## 1. Applicable GMP Standard

CONTRACT ACCEPTOR shall manufacture the SUBSTANCE(s) listed in Appendix X in compliance with cGMP.

“Current Good Manufacturing Practices” (cGMP) means all applicable standards relating to the manufacture of the SUBSTANCE(s) listed in Appendix X. For the purposes of this agreement, cGMP shall mean the principles (i) described in the ICH Q7 Guide, (ii) promulgated by any Governmental Authority having jurisdiction over the manufacture of the SUBSTANCE(s), in the form of laws or guidance documents, where the guidance documents are to be implemented within the pharmaceutical manufacturing industry for such SUBSTANCE(s).

*Note 1.1: if “regulatory“ and “GMP“ starting materials differ, the information on the start of GMP might be given here.*

## 2. Certificate of Analysis / Conformance (optional)

The following documentation is required for batches of SUBSTANCE shipped to CONTRACT GIVER:

- Certificate of Analysis and Conformance (optional) for each batch, issued by the independent Quality Unit
- Copies of investigation reports regarding quality incidents (critical deviations, OOS results, or similar), as applicable (see section 20)

The Certificates of Analysis and Conformance (optional) shall be dated and signed by a responsible person of the CONTRACT ACCEPTOR’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. The Certificate of Analysis states that the batch is suitable for release, and it must include – as a minimum –

- CONTRACT ACCEPTOR name and address, incl. telephone number (original manufacturing site),
- SUBSTANCE name and grade (if applicable),
- CONTRACT ACCEPTOR 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 SUBSTANCE.

*Note 2.1: the date of manufacture is considered as optional.*

### Optional:

The Certificate of Conformance states that the subject lot was produced in accordance to the applicable DMF, CEP or pharmacopoeial monograph(s), to the agreed manufacturing process, and in compliance with all applicable cGMP requirements as well as this Quality Agreement.

Certificate of Analysis and Certificate of Conformance may be issued as separate documents or combined to a single document, as appropriate.

*Note 2.2: the Certificate of Analysis may be attached as an appendix; in any case it should match the SUBSTANCE specification.*

### 3. Change Control

The CONTRACT ACCEPTOR shall have a documented and effective change control system in place and is required to provide advanced notification to the CONTRACT GIVER of any significant changes to the process, specifications and analytical methods (SUBSTANCE, intermediates and raw materials), storage, labelling and primary packaging, and equipment, which may have an impact on the quality of the SUBSTANCE, and/or on any regulatory applications related to the SUBSTANCE, if possible at least    (X) months in advance, to allow CONTRACT GIVER to assess the impact of the change upon the SUBSTANCE supplied or its use by CONTRACT GIVER.

#### Principles:

- ❑ SUBSTANCE produced by the new process shall not be accepted unless the process change has first been reviewed and delivery of SUBSTANCE approved by CONTRACT GIVER.
- ❑ Change requests should be supported by appropriate technical documents to support the change and to confirm that technical performance has not been altered.
- ❑ Modifications relating to SUBSTANCE specifications should only take place by a mutual consent between the two parties.
- ❑ For those changes required to comply with applicable laws and regulatory agency requirements, CONTRACT ACCEPTOR shall notify CONTRACT GIVER of such requirements after the CONTRACT ACCEPTOR becomes aware of the need for such change.
- ❑ CONTRACT GIVER shall assess any change request received from CONTRACT ACCEPTOR in a timely manner. Unless there are justified scientific reasons to reject the change request, or regulatory implications why CONTRACT GIVER may not want to pursue the proposed change, CONTRACT GIVER will not unreasonably withhold its approval of the request.
- ❑ CONTRACT GIVER is responsible for the submission of all necessary change notifications to all competent authorities in full compliance with the applicable regulations, respectively.

- CONTRACT GIVER will inform CONTRACT ACCEPTOR of the receipt of the necessary acknowledgement of the validity of the notification and, depending on the type of change, the acceptance or approval of the change by the competent authorities.

#### 4. Right to Audit

The CONTRACT ACCEPTOR shall allow ~~upon signature of a special confidentiality agreement~~ CONTRACT GIVER or its representatives to carry out on-site audits by appointment. The CONTRACT ACCEPTOR shall permit all reasonable access to the manufacturing, packaging, warehousing and laboratory areas related to the manufacture of the SUBSTANCE(s), including pertinent documentation. Any such audit shall take place during normal business hours and must not interfere with CONTRACT ACCEPTOR's manufacturing operations.

The results of the audit and the observation(s) shall be sent to the CONTRACT ACCEPTOR by means of a written report. The CONTRACT ACCEPTOR must ensure a satisfactory follow up to the observations made during the audit performed by the CONTRACT GIVER, and take corrective actions mutually agreed upon by the parties.

*Note 4.1: target timelines for both report and response may be added; a 4-weeks period is quite common, respectively.*

The audit frequency shall depend upon the results of the previous audit(s) and the quality performance of the CONTRACT ACCEPTOR. In the absence of critical quality incidents the frequency shall be not more than once every  (X) years. If quality issues arise CONTRACT GIVER shall have the right to audit more frequently.

*Note 4.2: in the absence of quality issues one audit every 3 years can be considered as industry standard.*

#### 5. Authority Inspections

The CONTRACT ACCEPTOR shall notify the CONTRACT GIVER of all regulatory authority inspections that are related to the SUBSTANCE, and that take place at the facility where the SUBSTANCE is manufactured or the testing laboratory where any of the associated testing is performed. If areas of concern exist which specifically involve the SUBSTANCE, CONTRACT GIVER should be notified prior to the inspection. In all other cases information on the results of the inspection is appropriate. Such notification will include

- Written notification of any observation, if any, that may impact the manufacture of the SUBSTANCE
- Written notification of all related corrective actions and planned completion dates
- Any further correspondence with the regulatory authority (if the manufacture of the SUBSTANCE is concerned)

### 6. Sub-contracting

6.1 CONTRACT ACCEPTOR agrees not to sub-contract to a third party or having done by a third party any of the work entrusted to them under this Quality Agreement without CONTRACT GIVER's prior written approval. If such an agreement is given, CONTRACT ACCEPTOR shall nonetheless 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. This must be assured through quality agreements with the respective sub-contractors and technical delivery specifications.

6.2 A list of currently approved sub-contractors related to the manufacture of the SUBSTANCE(s) is provided in Appendix X. In case that CONTRACT ACCEPTOR would like to use a new sub-contractor this list needs to be updated and is subject of approval by CONTRACT GIVER. Any change in sub-contracting shall follow the established change control procedure.

*Note 6.1: although "distribution" is part of "manufacture" as to the definition given in the ICH Q7 guideline it is understood that the use of contractors for transportation (haulers) is not in the scope of this section.*

### 7. Retention of samples (SUBSTANCE)

*Note 7.1: one of the two conditions given in 7.1 should be chosen, depending if an expiry date or a retest date has been defined for the SUBSTANCE.*

7.1 CONTRACT ACCEPTOR will store SUBSTANCE retention samples, sufficient to perform at least two (2) full specification analyses, in containers that are equivalent to or more protective than the commercial packaging. Samples are to be retained for < one (1) year after the expiry date of the batch assigned by SUPPLIER or for three (3) years after distribution, which ever is the longer > or < for three (3) years after the batch is completely distributed by SUPPLIER >.

*Note 7.2: "specification analysis" means "analysis according to the agreed specification" that may be identical with "compendial analysis" (if specification is equivalent to current pharmacopoeial monograph), or different in case there is no pharmacopoeial monograph, or if the agreed specification exceeds the monograph.*

Samples should be labelled, at least, with the following information:

- SUBSTANCE name
- CONTRACT ACCEPTOR batch/lot number
- Date of manufacture

7.2 CONTRACT ACCEPTOR will make SUBSTANCE retention samples available to CONTRACT GIVER promptly upon CONTRACT GIVER's justified request.

7.3 CONTRACT ACCEPTOR shall keep available any retention samples relevant to assessing the quality of the SUBSTANCE(s) in the event of complaints and/or recall procedures. This requirement shall continue even in case of termination of the supply of SUBSTANCE(s). In such a case CONTRACT ACCEPTOR may choose to deliver all samples to CONTRACT GIVER instead of keeping them for the required period.

### 8. Retention of records/documentation

*Note 8.1: one of the two conditions given in 8.1 should be chosen, depending if an expiry date or a retest date has been defined for the SUBSTANCE.*

8.1 CONTRACT ACCEPTOR will store the original master batch records, the executed batch records, and all other original documentation that is related to the manufacture of the SUBSTANCE and that is required to be maintained under cGMPs, protected from destruction and unauthorised access, for < one (1) year after the expiry date of the batch assigned by CONTRACT ACCEPTOR or for three (3) years after distribution, which ever is the longer > or < for three (3) years after the batch is completely distributed by CONTRACT ACCEPTOR >.

8.2 CONTRACT ACCEPTOR will retain the original manufacturing records for validation batches for the entire term of the contract manufacturing agreement. Upon termination of the contract manufacturing agreement, CONTRACT ACCEPTOR will provide CONTRACT GIVER with the original manufacturing records for validation batches. [Note: any other individual agreement between the parties would also be appropriate.]

8.3 Upon CONTRACT GIVER request, CONTRACT ACCEPTOR will promptly make copies of the original records available for CONTRACT GIVER.

8.4 CONTRACT ACCEPTOR will offer CONTRACT GIVER the option to take over the documents before destruction after X years.

8.5 CONTRACT ACCEPTOR shall keep available any records relevant to assessing the quality of the SUBSTANCE(s) in the event of complaints and/or recall procedures. This requirement shall continue even in case of termination of the supply of SUBSTANCE(s). In such a case CONTRACT ACCEPTOR may choose to deliver all documents to CONTRACT GIVER instead of keeping them for the required period.

### 9. Stability

*Note 9.1: the level of detail in this section will depend upon how much control the contract giver wants over the contract acceptor. Usually the contract giver desires control over stability protocol/methods/specs as well as access to all data for regulatory submissions.*

CONTRACT ACCEPTOR will perform stability studies for the SUBSTANCE(s) as per ICH guidelines and CONTRACT GIVER requirements.

CONTRACT ACCEPTOR is responsible for assigning re-evaluation dates to the SUBSTANCE(s) and for determining suitable storage and shipping conditions, based upon stability studies.

CONTRACT ACCEPTOR is responsible for generating stability protocols, methods and specifications.

CONTRACT GIVER is responsible for approving stability protocols, methods and specification.

CONTRACT ACCEPTOR will upon request or at least annually provide updated data from the stability program (initial or on-going studies) to CONTRACT GIVER.

CONTRACT ACCEPTOR will inform CONTRACT GIVER if there are any adverse trends that could impact on current retest date.

### **10. Complaints**

All complaints related to the SUBSTANCE(s) reported, regardless of source (e.g., consumers, doctors, pharmacists, sales representatives) will be handled by CONTRACT GIVER and communicated to CONTRACT ACCEPTOR.

CONTRACT ACCEPTOR is responsible for recording and investigating all quality-related complaints on the SUBSTANCE and will maintain the complete complaint database and complaint files.

CONTRACT ACCEPTOR will complete their investigation and respond to CONTRACT GIVER in writing to all complaints within 20 business days of receipt.

A formal written report on the complaint detailing identifiable root causes and corrective and preventive actions where applicable shall be prepared by CONTRACT ACCEPTOR and sent to the CONTRACT GIVER.

In case the investigation could not be finalized within 20 business days, CONTRACT ACCEPTOR will provide an interim report to CONTRACT GIVER.

*Note 10.1: individual (target) timelines for both initial and concluding responses may be set by the parties; for the concluding response a period of 20 business days is quite common.*

CONTRACT ACCEPTOR is responsible for implementing a corrective action plan to correct any deficiencies identified during an investigation.

The CONTRACT GIVER will make relevant information and samples of the affected SUBSTANCE(s) available to assist in the investigation of the CONTRACT ACCEPTOR.

### **11. Recall**

In the event that the CONTRACT ACCEPTOR believes that a recall of the SUBSTANCE(s) maybe necessary or appropriate, the CONTRACT ACCEPTOR shall immediately notify the CONTRACT GIVER. The two parties will take joint decisions on the disposition of SUBSTANCE or (if applicable) finished drug product made thereof or user information, where required.

The CONTRACT GIVER is responsible for the final decision and the coordination of any recalls or field alert activities.

The CONTRACT ACCEPTOR shall provide any information required by the CONTRACT GIVER relating to recall or field alert activities within two (2) business days of the request, if such information is readily available at the CONTRACT ACCEPTOR.

The CONTRACT ACCEPTOR will not initiate any notifications to health authorities concerning a (potential) non-conformance without the prior agreement of CONTRACT GIVER.

The CONTRACT ACCEPTOR will collaborate, if needed, in any recall of a defective batch of SUBSTANCE.

### 12. Product quality review

CONTRACT ACCEPTOR shall conduct an annual Product Quality Review (PQR) for the SUBSTANCE(s), according to the requirements of ICH Q7 and any additional requirements mutually agreed between the parties.

*Note 12.1: a reference to an appendix specifying such additional requirements might be included, if applicable. Since the PQR as to ICH Q7 is usually applicable to commercial products, the parties should define how to handle in case of development products.*

CONTRACT ACCEPTOR will provide CONTRACT GIVER with copies of the relevant information of its PQR of the previous annual period,

- Option 1: upon request, within a reasonable timeframe.

- Option 2: within any timeframe mutually agreed between the parties.

- Option 3: within 3 months from the closure of the annual period.

CONTRACT GIVER shall fulfil any regulatory requirements of regulatory authorities related to the PQR for drug products manufactured from the SUBSTANCE(s).

### 13. Storage and distribution

*Notes:*

*13.1: Storage: special storage requirements for the SUBSTANCE(s) should be clear.*

*13.2: Distribution: either in the Supply Agreement or in the Quality Agreement the responsibilities for the whole supply chain should be defined; reference to GDP (IPEC, WHO) is recommended. Usually the CONTRACT ACCEPTOR is responsible for the transportation from the manufacturing site to the CONTRACT GIVER's receiving site. The following text is written in this sense (to be changed, if responsibilities are different).*

CONTRACT ACCEPTOR shall make commercially reasonable efforts to exclude, during packaging, storage, and shipping of the SUBSTANCE(s), the possibility of deterioration, contamination, or mix-ups with any other material.

CONTRACT ACCEPTOR shall comply with the following requirements in relation to distribution of the SUBSTANCE(s).

- Distribution in accordance with storage conditions stated on the labels
- Contracts with hauliers and shipping agents
- Ability to recall SUBSTANCE from distribution network
- Quarantine SUBSTANCE with questionable quality
- Utilise tamper evident seals on all packaging
- CONTRACT ACCEPTOR will qualify hauliers and shipping agents used to transport the SUBSTANCE(s). The list of approved hauliers and shipping agents shall be maintained in Appendix X.

CONTRACT ACCEPTOR will send a Certificate of Analysis with each shipment of SUBSTANCE and independently send one to <list recipients here>.

CONTRACT ACCEPTOR will provide an up-to-date MSDS to CONTRACT GIVER with each shipment or at least on an annual basis.

### 14. Undesirable contaminants

*Note 14.1: the three items listed below constitute the most frequently requested ones. Others may be added as appropriate.*

#### 14.1 BSE/TSE

CONTRACT ACCEPTOR shall provide to CONTRACT GIVER a BSE/TSE certificate for the SUBSTANCE(s) listed in accordance with the EMEA Note for Guidance EMEA/410/01 (current revision). The certificate shall indicate if the SUBSTANCE(s) is (are) of human or animal origin, and if materials of human or animal origin are used during the manufacturing process of the SUBSTANCE(s). An updated BSE/TSE certificate must be issued after any change to the manufacturing process which involves new raw materials or for raw materials that have been sourced from a different supplier.

#### 14.2 Residual solvents

SUPPLIER shall provide to CUSTOMER a residual solvents statement for the SUBSTANCE(s) listed in accordance with the ICH Q3C guideline. An updated statement must be issued after changes to the manufacture of the SUBSTANCE(s), if applicable.

#### 14.3 Metal catalyst/reagent residues

SUPPLIER shall provide to CUSTOMER a statement on metal residues for the SUBSTANCE(s) listed in accordance with the EMEA “*Guideline on the specification limits for residues of metal catalysts or metal reagents*” (EMEA/ CHMP/ SWP/ 4446/ 2000) and other applicable regulations. An updated statement must be issued after changes to the manufacture of the SUBSTANCE(s), if applicable.

### 15. HAPIs

15.1 CONTRACT ACCEPTOR shall ensure that its facilities are used in line with any authorizations for HAPIs granted by the competent regulatory authority.

15.2 CONTRACT ACCEPTOR shall not conduct production and handling of highly sensitizing materials (such as penicillins or cephalosporins) in the equipment being used for the SUBSTANCE(s). Production of such materials in the same building being used for the SUBSTANCE(s) is permitted only if performed in a closed and dedicated system.

15.3 CONTRACT ACCEPTOR shall not conduct the production of certain additional products, such as certain highly active or toxic drugs and non-medicinal products in the same equipment used for the SUBSTANCE(s). For those products, in exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and validated inactivation and/or cleaning procedures are in place.

#### Optional:

In case CONTRACT ACCEPTOR intends to conduct production of any such product in the same equipment used for the SUBSTANCE(s), it shall provide CONTRACT GIVER with the necessary information to allow CONTRACT GIVER a proper risk assessment. CONTRACT GIVER will then approve or reject CONTRACT ACCEPTOR’s request on a scientific basis.

## 16. Raw materials

*Note 16.1: certain grades or qualities of raw materials may be defined; special requirements with respect to the storage period of retention samples of materials may be stipulated (particularly in development).*

CONTRACT ACCEPTOR shall be responsible for the purchase, storage, handling, sampling, testing and approval or rejection of materials used in manufacturing the SUBSTANCE(s) pursuant to this agreement, with the exception of any material supplied by CONTRACT GIVER.

CONTRACT ACCEPTOR shall implement a vendor qualification program for evaluating the suppliers of critical materials, with the only exception of materials supplied by CONTRACT GIVER. CONTRACT ACCEPTOR shall only purchase materials from qualified suppliers.

CONTRACT ACCEPTOR must utilize documented material inspection plans and testing procedures. The results of this inspection and testing must be in accordance with specifications filed by CONTRACT GIVER.

CONTRACT ACCEPTOR will inspect and/or test all materials on a batch-by-batch basis.

Raw materials supplied by qualified vendors and those supplied by CONTRACT GIVER can be subject to reduced testing but a minimum ID testing (or visual examination in case of hazardous or highly toxic raw materials) needs to be performed for each delivery and each lot.

CONTRACT ACCEPTOR shall store and handle materials used in manufacturing the SUBSTANCE(s) pursuant to this agreement under appropriate conditions, consistent with cGMPs, all applicable laws, rules and regulations, and industry standards. CONTRACT GIVER shall inform CONTRACT ACCEPTOR on the storage conditions of any material supplied to CONTRACT ACCEPTOR.

CONTRACT ACCEPTOR shall have all necessary and appropriate controls in place to prevent cross-contamination of the raw materials and intermediates used in the manufacture of the SUBSTANCE(s) from other chemicals stored, used, or manufactured by CONTRACT ACCEPTOR, including but not limited to potent hormones, cytotoxic compounds, beta-lactams, highly potent drugs, biological preparations or non-pharmaceutical chemicals.

### Optional (if applicable):

CONTRACT GIVER shall supply CONTRACT ACCEPTOR with enough amount of intermediate to manufacture the quantities of batches ordered. CONTRACT GIVER warrants that any intermediate supplied to CONTRACT ACCEPTOR shall comply with the agreed specifications. A Certificate of Analysis shall be submitted by CONTRACT GIVER to CONTRACT ACCEPTOR and shall accompany each shipment. The specification in force for the intermediate is attached as Appendix X. CONTRACT GIVER shall be responsible for the maintenance and storage of appropriate retain samples of any material supplied to CONTRACT ACCEPTOR.

If CONTRACT ACCEPTOR believes that any shipment of intermediate does not meet specification he will notify it to CONTRACT GIVER in writing, including a detailed explanation of the non-conformity. CONTRACT GIVER shall investigate such alleged non-conformity and, if agrees, such intermediate is non-conformance and CONTRACT GIVER will replace the material or the SUBSTANCE(s) will be manufactured at the sole risk of

CONTRACT GIVER. If CONTRACT GIVER disagrees it will notify it to CONTRACT ACCEPTOR in writing. Manufacturing of the SUBSTANCE(s) will be at the sole risk of CONTRACT GIVER. CONTRACT ACCEPTOR shall not be responsible of intermediate's defects or not meeting specifications.

### 17. Qualification / Validation

Equipment qualification, process validation, analytical methods validation and validation of computerized systems, if used, are in place and covered by change control. Validation documentation shall be available for review during an audit. On request, the CONTRACT GIVER will get copies or summaries from the validation reports.

**Development:**

Equipment qualification and change control in place. Verification of analytical methods for intended use (see Note).

*Note: in some cases, e.g. in case SUBSTANCE lots will be used for clinical phase 3 studies, or prior to the validation campaign at the latest, the analytical methods should be validated according guidelines.*

### 18. Reprocessing

Reprocessing shall be performed according to the current regulatory dossier and reported to the CONTRACT GIVER. Reasons for reprocessing have to be investigated, and the results shall be communicated with the CONTRACT GIVER.

**Development:**

Reprocessed batches have to be reported and agreed with the CONTRACT GIVER.

### 19. Reworking

Reworking is only possible after approval by CONTRACT GIVER. Any reworking process should be validated. Additional stability tests and analytical testing of reworked batches may be required.

**Development:**

Reworked batches have to be reported and approved by CONTRACT GIVER. Reworking process could be part of the experience through process development.

### 20. Deviations / OOS (incl. stability)

CONTRACT ACCEPTOR will notify CONTRACT GIVER promptly in the event of any critical deviation(s) that can potentially affect the integrity of the SUBSTANCE(s). Any advice by CONTRACT GIVER on the handling of the deviation or the affected material (e.g., on root cause analysis or corrective actions) shall be given promptly so that further production is not unreasonably hindered.

## APIC Quality Agreement Template (Exclusive Substances)

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CONTRACT ACCEPTOR will forward a copy of the completed report on any full-scale OOS investigation to CONTRACT GIVER within a reasonable period of time.

For all confirmed OOS stability test results that indicate that the SUBSTANCE(s) has (have) failed to remain within specifications, CONTRACT ACCEPTOR will notify CONTRACT GIVER promptly and provide the stability data.

CONTRACT GIVER may participate in any full-scale investigation concerning OOS results.

CONTRACT ACCEPTOR will implement any agreed actions arising out of the completed investigation report in order to avoid the reoccurrence of similar issues in the future.

### 21. Packaging

In addition to the requirements in ICH Q7 the following shall apply to the packaging of the SUBSTANCE(s):

The specifications for packaging materials including tamper evident seals must be in accordance with the regulatory documentation related to the SUBSTANCE(s).

CONTRACT ACCEPTOR shall package the SUBSTANCE(s) using the components, closures and tamper evident seals as specified in Appendix X.

*Note 21.1: the list in Appendix X may include both primary packaging materials and secondary ones, e.g. pallets, wrapping etc. There may be the need to define and explain any coding on the seals.*

< List other security measures here (as applicable). >

*Note 21.2: the following paragraph is only applicable in very specific cases.*

#### Optional:

When primary packaging material is returned from CONTRACT GIVER to CONTRACT ACCEPTOR for reuse, CONTRACT ACCEPTOR will validate the cleaning procedure(s) used to clean the packaging material.

CONTRACT ACCEPTOR shall apply suitable traceability to primary packaging materials such that the manufacturer's batch can be traced from the batch of the SUBSTANCE(s) supplied.

### 22. Labelling

#### Notes:

22.1: the shipping label may include additional information (e.g., CONTRACT GIVER material code); details may be defined in the Supply Agreement;

22.2: labelling should be described if done on behalf of the CONTRACT GIVER;

22.3: an example of the label may be provided in the appendix.

CONTRACT ACCEPTOR shall comply with the requirements in ICH Q7 in relation to labelling, in particular:

- Labelling operations shall be conducted to prevent mix ups,

- Labels shall be checked for accuracy before application,

This agreement does not absolve the CONTRACT ACCEPTOR from complying with any legal requirements in relation to the transportation of the SUBSTANCE(s).

In addition the following shall apply to the labelling for the SUBSTANCE(s):

**Optional:**

**CONTRACT ACCEPTOR shall indicate the retest date on the SUBSTANCE label.**

CONTRACT ACCEPTOR shall use the following batch/lot number format <xxyyzz> where <xx> means <...> and <yy> .....

### **23. Regulatory documents**

CONTRACT GIVER shall be responsible for preparation of registration documents related to SUBSTANCE and finished drug products made from the SUBSTANCE and submission of such registration documents to any regulatory authority, including maintaining such submissions (hereafter altogether called 'Regulatory Submissions').

Upon request by, and in mutual consultation with CONTRACT GIVER, CONTRACT ACCEPTOR shall be responsible for preparation of documentation on manufacture of SUBSTANCE as required for the Regulatory Submissions of CONTRACT GIVER, limited to CONTRACT ACCEPTOR's activities under this agreement.

CONTRACT GIVER shall provide portions of Regulatory Submissions, related to SUBSTANCE and CONTRACT ACCEPTOR's activities performed under this agreement, to CONTRACT ACCEPTOR for review and written consent, prior to submission to any regulatory authority.

CONTRACT ACCEPTOR shall review and comment to CONTRACT GIVER on such portions of Regulatory Submissions, within [ ] business days from receipt.

CONTRACT GIVER shall, upon submission to any regulatory authority, provide CONTRACT ACCEPTOR with current copies of portions of Regulatory Submissions, including amendments and supplements thereto, related to the SUBSTANCE and CONTRACT ACCEPTOR's activities performed under this agreement.

CONTRACT ACCEPTOR will provide, in mutually agreed timelines, all other information related to the SUBSTANCE that CONTRACT GIVER may reasonably request for its Regulatory Submissions, including any data for annual reports (e.g. annual stability reports for the SUBSTANCE).

When a change is known to require, or has the potential to require a Regulatory Submission, CONTRACT GIVER will develop a joint strategy to obtain the appropriate regulatory approvals prior to implementation of the change. For change control see section 3.

### **24. Product release**

CONTRACT ACCEPTOR has the responsibility to release the SUBSTANCE(s) for shipment to the CONTRACT GIVER.

*Note 24.1: alternatively, the CONTRACT ACCEPTOR may provide a pre-shipment sample to the CONTRACT GIVER. The CONTRACT GIVER will test that sample, and if OK, will give its approval for shipment to the CONTRACT ACCEPTOR.*

CONTRACT ACCEPTOR will not ship any SUBSTANCE to any destination, as identified by the CONTRACT GIVER, until the SUBSTANCE is released for shipment, unless prior written approval has been received from the CONTRACT GIVER to perform such a shipment under quarantine.

CONTRACT ACCEPTOR is responsible for the issuance for each batch of SUBSTANCE a Certificate of Analysis and Certificate of Conformance (delete, if not appropriate; see also section 2).

**Optional:**

CONTRACT GIVER may, in its sole discretion, delegate the final release authority for the SUBSTANCE(s) to CONTRACT ACCEPTOR. CONTRACT GIVER reserves the right to withdraw the delegated final release authority from CONTRACT ACCEPTOR at any time.

### 25. Reference standards

All reference standards should be stored in accordance with the suppliers recommended storage conditions and used within their given expiry or retest date.

CONTRACT ACCEPTOR or CONTRACT GIVER (delete as appropriate) is responsible for the purchase and certification of the reference standards.

(In case, CONTRACT ACCEPTOR is responsible) CONTRACT ACCEPTOR shall provide to CONTRACT GIVER reasonable quantities of any non-compendial or not commercially available reference standards necessary to perform the tests included in the SUBSTANCE specification.

(In case, CONTRACT GIVER is responsible) CONTRACT GIVER shall provide to CONTRACT ACCEPTOR reasonable quantities of any non-compendial or not commercially available reference standards necessary to perform the tests included in the SUBSTANCE specification.

### 26. Specifications

Specifications for the SUBSTANCE(s), intermediates, key raw materials and packaging components, as applicable, are detailed in Appendix X.

Any significant changes to these specifications must be approved by the CONTRACT GIVER via a formal change control system (see section 3).

### 27. Analytical methods

Analytical methods used for testing the SUBSTANCE(s): compendial analytical methods must be verified and all others must be validated prior to use.

Development:

Verification of analytical methods for intended use (see Note).

*Note: in some cases, e.g. in case SUBSTANCE lots will be used for clinical phase 3 studies, or prior to the validation campaign at the latest, the analytical methods should be validated according guidelines.*

Any significant changes to these analytical methods must be approved by the CONTRACT GIVER via a formal change control system (see section 3).

## **28. Manufacturing**

CONTRACT ACCEPTOR shall have appropriate control procedures in place to ensure that only authorised personnel has access to CONTRACT ACCEPTOR's manufacturing facilities.

*Note 28.1: more stringent acceptance criteria for cleaning may be agreed between both parties if requested by CONTRACT GIVER. Such special agreements should be included here.*

**Annex: Division of Responsibilities**

[ CG = CONTRACT GIVER; CA = CONTRACT ACCEPTOR ]

<b>A Regulatory Compliance</b>		<b>CG</b>	<b>CA</b>
1.	Adhere to approved registration documentation (Marketing Authorisation, NDA, IND, DMF, CEP, etc, as applicable)	X	X
2.	Maintaining valid manufacturing license(s), as applicable		X
3.	Maintaining site master file, as applicable		X
4.	Approving significant changes	X	
5.	Submitting change notifications/applications to authorities	X	

<i>Note: if necessary and agreed by the parties, responsibilities with respect to purchasing, manufacturing, and testing of materials and intermediates <u>before</u> the API SMs may be added here</i>		
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<b>B Purchasing, Manufacturing and Analytical Testing of API Starting Materials (SMs), Raw Materials, Process Aids, and Intermediates after API SMs, and SUBSTANCE</b>		<b>CG</b>	<b>CA</b>
6.	Setting specifications for SUBSTANCE	X	
7.	Setting specifications for materials and intermediates	Review	X
8.	Purchasing materials according to specifications		X
9.	Qualifying and monitoring material suppliers		X
10.	Performing an identity check on incoming material		X
11.	Testing of incoming material, as appropriate		X
12.	Generating Master Batch Procedure/Record		X
13.	Approving Master Batch Procedure/Record	Final approval	X
14.	Manufacturing SUBSTANCE according to Master Batch Procedure (incl reprocessing, packaging, labelling)		X
15.	Generating Batch Production Record		X
16.	Approving Batch Production Record	Final approval	X
17.	Assigning batch numbers		X
18.	Sampling of incoming materials		X
19.	Sampling during production of SUBSTANCE (incl API, if applicable)		X
20.	Developing analytical test-methods for in process controls (IPCs)		X
21.	Setting specifications for IPCs		X

## APIC Quality Agreement Template (Exclusive Substances)

<b>B Purchasing, Manufacturing and Analytical Testing of API Starting Materials (SMs), Raw Materials, Process Aids, and Intermediates after API SMs, and SUBSTANCE</b>		<b>CG</b>	<b>CA</b>
22.	Performing IPCs		X
23.	Developing and writing analytical test methods for API SMs, raw materials, process aids, intermediates, and SUBSTANCE		
24.	Validating analytical test methods for API SMs, raw materials, process aids, intermediates, and SUBSTANCE, according to CG expectations		
25.	Approving analytical test methods and validation protocols and reports	Final approval	X
26.	Transferring validated analytical methods to CA	X	
27.	Releasing SUBSTANCE (according to specifications and based on CoA testing) for shipment to CG		X
28.	Deciding on final disposition of SUBSTANCE	X	
29.	Defining amount for retention samples	X	
30.	Storing retention samples, until shipment to CG (if requested)		X
31.	Investigating OOS results and critical deviations	Review and final approval	X
32.	Approving analytical records for the SUBSTANCE	Final approval	X
33.	Disposing not used materials, intermediates or SUBSTANCE in an environmentally safe manner		X
34.	Purchasing / providing of (certified) reference standards		

<b>C Purchasing and Testing of Packaging Material</b>		<b>CG</b>	<b>CA</b>
35.	Specifying packaging material for SUBSTANCE	X	
36.	Specifying packaging material for materials before the SUBSTANCE, if needed		X
37.	Developing test methods for primary packaging material, if needed		X
38.	Purchasing packaging material		X
39.	Testing and releasing primary packaging material		X
40.	Taking retention samples of primary packaging material		X
41.	Purchasing tamper evident seals for containers to be shipped to CG		X

## APIC Quality Agreement Template (Exclusive Substances)

<b>D Labelling, Label Printing and Label Reconciliation (at CA)</b>		<b>CG</b>	<b>CA</b>
42.	SUBSTANCE		X
43.	Materials and intermediates		X
44.	Samples		X
45.	Waste		X

<b>E Storage and Shipment</b>		<b>CG</b>	<b>CA</b>
46.	Storing SUBSTANCE under labelled conditions	X	X
47.	Qualifying of carrier		
48.	Preparing SUBSTANCE for dispatch and loading of vehicles		X
49.	Maintaining storage conditions during transportation until agreed transition point		X

<b>F Documents (Generation and Approval)</b>		<b>CG</b>	<b>CA</b>
50.	Establishing synthesis scheme (including definition of API SMs)	X	
51.	Generating Master Batch Procedure/Record	(ref. to table B)	
52.	Approving Master Batch Procedure/Record	(ref. to table B)	
53.	Generating Batch Production Record	(ref. to table B)	
54.	Approving Batch Production Record	(ref. to table B)	
55.	Archiving the original documents and sending copies to CG		X
56.	Updating safety data sheet of intermediates and SUBSTANCE, as soon as further relevant information becomes available	X	X
57.	Providing Certificates of Analysis and BSE/TSE statements of materials supplied by CG	X	
58.	Providing suppliers' certificates concerning TSE and origin of raw materials and process aids procured and used by CA		X
59.	Issuing Certificate of Analysis for SUBSTANCE for shipment to CG		X
60.	Issuing Certificate of Analysis of SUBSTANCE for final disposition (e.g., technical, toxicological or human use)	X	
61.	Issuing notifications on atypical results (e.g., OOE)	Review	X
62.	Issuing reports on full-scale OOS investigations and critical deviations	Review or approval	X
63.	Providing development reports, test procedures, validation documents, etc and other source documents requested by CG	Review	X

## APIC Quality Agreement Template (Exclusive Substances)

<b>G Equipment Cleaning</b>		<b>CG</b>	<b>CA</b>
64.	Sharing information on toxicity of SUBSTANCE and raw materials, process aids and intermediates, if available	X	X
65.	Establishing solubility of SUBSTANCE and intermediates in cleaning agent used	X	X
66.	Assessing/verifying cleanliness of used equipment		X
67.	Releasing equipment after cleaning		X

<b>H Qualification / Validation</b>		<b>CG</b>	<b>CA</b>
68.	Qualifying of equipment, utilities and facilities		X
69.	Preparing and approving equipment and facility qualification protocols and reports used for the SUBSTANCE(s)		X
70.	Validating the manufacturing process		X
71.	Preparing and approving process validation protocols and reports for the SUBSTANCE(s)	Final approval	X
72.	Validating cleaning procedures		X
73.	Preparing and approving cleaning validation approach applicable to the SUBSTANCE(s)	Final approval	X
74.	Validating analytical methods		X
75.	Preparing and approving analytical validation approach applicable to the SUBSTANCE(s)	Final approval	X
76.	Retaining qualification and validation documentation		X
77.	Validating computerised systems		X
78.	Preparing and approving validation protocols and reports for computer validation		X

<b>I Stability Program</b>		<b>CG</b>	<b>CA</b>
79.	Preparing stability protocol		X
80.	Approving stability protocol	Final approval	X
81.	Performing stability study under ICH conditions (incl testing)		X
82.	Reviewing stability data and determining retest period	Review	X
83.	Preparing stability report		X
84.	Approving stability report	Final approval	X
85.	On-going stability studies		X

## APIC Quality Agreement Template (Exclusive Substances)

<b>K Product Quality Review</b>		<b>CG</b>	<b>CA</b>
86.	Preparing annual PQR report		X
87.	Reviewing PQR reports	X	X

<b>L Complaints and Recall</b>		<b>CG</b>	<b>CA</b>
88.	Receiving complaints from external customers	X	
89.	Forwarding complaints related to SUBSTANCE to CA	X	
90.	Investigating complaints related to SUBSTANCE		X
91.	Implementing corrective actions, if necessary	Review	X
92.	Responding to external customers	X	
93.	Deciding to initiate recall	X	
94.	Notifying authorities, external customers, or consumers	X	X <sup>1)</sup>
95.	Clarifying root cause	X	X
96.	Storing or disposing returned product	X	X <sup>2)</sup>

<sup>1)</sup> Responsibility to notify local authority in the country of manufacture of SUBSTANCE, if applicable

<sup>2)</sup> Responsibility regarding SUBSTANCE only

<b>M Sub-Contracting</b>		<b>CG</b>	<b>CA</b>
97.	Approving sub-contracting operations	X	
98.	Qualifying sub-contractor		X
99.	Procuring of sub-contracted products or services		X
100.	Quality monitoring sub-contracted operation		X