

1. Purpose

The purpose of this Guideline is to define the general requirements and provide guidance for Quality Agreements for the development, manufacture, testing, storage and distribution of intermediates, active pharmaceutical ingredients and investigational products destined for use in pre-clinical, clinical and other Research and Development studies.

2. Scope and Applicability

This Guideline applies to cGMP activities for any relevant site. It is applicable to the provision of a service, product, project and study (hereafter called “service”) of any site and also to external providers of those services. The guideline also provides recommendations about when an Agreement between two parties should be considered but is not a definitive nor exhaustive list and the need for an Agreement for a particular service should be considered on a case by case basis.

3. Definitions

3.1 Quality Agreement (Contractual Agreement)

A written and binding agreement between a Contract Giver and Contract Acceptor which clearly defines the roles and responsibilities of each party in the provision of a service to ensure that all quality attributes consistently meet the contract giver’s and cGMP requirements.

3.2 Contract Giver (“GIVER”)

A person or entity who on behalf of the site, commissions a service, product, project or study.

3.3 Contract Acceptor (“ACCEPTOR”)

A person or entity who agrees to provide the contract giver with a service, product, project or study according to the givers specified requirements.

3.4 Confidentiality Agreement (Secrecy Agreement)

A legal document prepared and approved jointly by the giver site and an external contract acceptor which defines the requirement for the provision of expertise, and technical information to undertake the service whilst maintaining the intellectual property rights of both parties, and approved by the legal functions within the giver site and the contract acceptor.

3.5 Technical Agreement

A document describing in sufficient detail, all relevant technical information to enable the service to be undertaken, in a safe manner, and in accordance with the requirements of giver site specifications or defined technical attributes. The

- to Outsourcing and Procurement.
- Assuring that the “acceptor” is able to meet the cGMP requirements relevant for the service.

5. Guideline

During the development of new products it is often necessary to use the manufacturing, testing, packaging or distribution facilities and capabilities of Operations site or of external contractors

Recommendations when an Agreement between two parties should be considered are given in Appendix 1. It is not a definitive nor exhaustive list and the need for an Agreement for a particular service should be considered on a case by case basis.

The Quality Agreement for both internal and external providers should include the following general aspects given in 5.1 below. Specific, additional guidance relevant to internal and external providers is described in 5.2 and 5.3 respectively.

When it is proposed to use a contractor during development that may be used for future commercial activities, i.e. a Strategic Contracted Supplier, there should be close collaboration between R&D, the New Product Manager, Project Team and for chemical intermediates and active pharmaceutical ingredients, Outsourcing and Procurement Group, to ensure that the contractor is acceptable for both development and commercial supply.

The Quality Agreement should be approved by the QA representatives at the respective sites on behalf of the “GIVER” and “ACCEPTOR”. In addition, the site functional representatives should also approve the Agreement. Where the “ACCEPTOR” does not have dedicated QA resource, then functional signatory includes approval for all aspects.

Within the EU and where an Agreement is prepared to define the responsibilities of Qualified Persons for different manufacturing steps of an Investigational Medicinal Product as required by Annex 16 of the EU GMP, the Agreement should be signed by a Qualified Person at the respective sites.

5.1 General Requirements

The following general aspects should be considered for inclusion in the Quality Agreement between “GIVER” and “ACCEPTOR”. The extent and detail may vary depending on the nature, complexity and the duration of the service provided. Where appropriate, a generic Agreement should be prepared which should describe the service to be undertaken, without the need to reference specific batches, studies or campaigns. This level of detail may be documented in specific, supplementary Work Orders, Plans or Schedules, which would be identified in the Agreement as providing this specific level of detail. When an Agreement is prepared by an Operations Site, or in some cases by an external provider, the style and format may differ but would be considered

If the transfer is to another development facility, then the transfer may be less formal but nonetheless should still be documented appropriate to the stage of development and competency by the receiving site to undertake the work should be established and/or documented.

In-process control tests should be defined where necessary and methodology supplied.

For analytical testing, procedures for investigating Out of Specification results should be defined.

5.9 Responsibilities for Review/Approval/Archiving of and Packaging Documentation

Responsibilities for the preparation, review and approval of master and executed Documentation for manufacture and packaging, should be defined.

Duplication of reviews and approvals should be avoided wherever possible, for example, review of an executed batch record by QA in addition to the QA of the service provider, whether the giver site or external contractor should be only be undertaken if there are specific quality and business needs to do so.

Responsibilities for archiving of the original documentation and copies, if taken, should be defined.

5.10 Product Release

Responsibility for product release of an API or investigational product destined for R&D purposes, lies with QA. If a commercial product, released by Operations QA for sale and is to be used for R&D use, it should be released by QA. Responsibilities for release of an API intermediate, normally destined for a sales product, should be defined in the Agreement and would normally be done by Operations QA.

Within the EU where different manufacturing steps for the manufacture/assembly of an Investigational Medicinal Product are conducted at different EU sites, responsibilities of each Qualified Person for each step, as required by Annex 16 of the EU GMP, should be defined in the Agreement, which should be approved by a Qualified Person at the respective sites.

5.11 Shipment and Distribution

Requirements for shipment and distribution where appropriate, including storage conditions of the finished material (intermediate stage of an API, the API or investigational product) to its destination, whether returned to the giver site or elsewhere in the supply chain should be defined.

development to ensure the contractor is acceptable for both development and commercial use.

- **Responsibilities for Review/Approval of manufacturing and Packaging Documentation**

Roles and responsibilities for review and approval of master and executed manufacturing and packaging documentation should be defined.

Master manufacturing and packaging documentation should be reviewed and approved by QA within the giver site to assure that all technical and cGMP requirements have been met in accordance with the giver site policies and standards.

Duplication of reviews and approvals should be avoided, however it is recommended that executed records should be reviewed by QA initially until assurance of the reviews undertaken by the provider is gained. For intermediate and API manufacture, the review by QA may not be possible but responsibilities should be defined in the Agreement.

- **Debarment List**

The service provider should not use anyone on a regulatory authority debarment list, for example, the FDA Debarment list, to perform work on behalf of the giver site

- **Regulatory Inspections**

The service provider should inform the giver site of any Regulatory inspections performed within their facilities and the outcome from such inspections. In some cases, prior notification of an inspection should be given where it may be likely that a product may be included in the scope of the inspection.

Where an adverse inspection outcome has occurred, the giver site should consider terminating the Agreement, unless assurance can be provided, of corrective actions, which are acceptable to the regulatory authority.

Preparations for Pre-Approval Inspections (PAIs), the service provide, in support of New Drug Applications, should involve close collaboration with the giver site, including pre PAI audits as appropriate.