

IPAC-RS Quality Agreement Template Toolkit

I. What is it?

This toolkit provides a template for quality agreements between manufacturers/developers of orally inhaled and nasal drug products (OINDP) and their suppliers, and between container closure component/device suppliers and their materials suppliers. The template provides general guidance on the typical elements of a Quality Agreement. Users can add or revise specific areas as appropriate to the situation and internal policies and procedures. Specific areas of the template provide reference to the IPAC-RS GMP Guideline¹ so that users can correlate the elements of a quality agreement to GMP concepts.

II. Who is it For?

This toolkit is for:

- Industry professionals developing a quality agreement for use with their suppliers or customers
- Industry professionals interested in learning more about the purposes and use of quality agreements and their foundation in GMP concepts and quality enhancement
- Regulators interested in learning more about the purposes and use of quality agreements and their foundation in GMP concepts and quality enhancement

III. Why Use It?

The Quality Agreement Template will:

- Help users to identify and understand the basic elements of a Quality Agreement required when addressing raw materials, container closure/device components, and packaging materials. Benefits include:
 - Assisting in harmonizing quality expectations between parties
 - Promoting and advancing implementation of Quality by Design concepts within the supply chain by raising awareness of how companies may practically build quality into their products through strong and robust quality systems and communication with their suppliers, customers and partners.

¹ International Pharmaceutical Consortium on Regulation and Science (IPAC-RS) Good Manufacturing Practices Guideline for Suppliers of Components for Orally Inhaled and Nasal Drug Products. 2006. The guideline can be ordered through the IPAC-RS website: <http://www.ipacrs.com/publications.htm>

Quality Agreement Template

(All Agreements should be controlled documents)

Please note that this document only presents examples of topics and issues that could be included in a Quality Agreement.

Between	Pharmaceutical OINDP Manufacturer or n-1 Supplier Address
And	n-1 Supplier or n-2 Supplier Address
On	Date of Quality Agreement

Note that for this Template, the following definitions apply:

Pharmaceutical OINDP Manufacturer Pharmaceutical company that develops and manufactures final OINDP.

n-1 Supplier Supplier of container closure and/or device components, packaging materials, to Pharmaceutical OINDP Manufacturer.

n-2 Supplier Supplier of raw materials or other materials or services to n-1 Supplier.

Contact Information

(May be included in a Contact Matrix, which may be included prominently on first page, or at end of Quality Agreement. See Appendix B for example)

Authorized Signatures

Party 1 _____ Party 2 _____

1. Purpose and Scope

Define the **purpose and scope** of the Quality Agreement. In general, the Quality Agreement should define the roles and responsibilities of the OINDP manufacturer and supplier with respect to quality and technical issues that ensure cGMP and define specific processes for ensuring clear and efficient communication between the parties. The Quality Agreement helps define the provider-customer relationship. Roles and responsibilities should be specifically summarized in a Responsibility Matrix (see Part 8, below, and Appendix A). If desired, technical issues can be addressed in more detail in a separate Technical Agreement, and referenced in the Quality Agreement.

Purpose and scope could include duration of Quality Agreement and general description of the products and/or services to which the Quality Agreement applies (e.g., identify the material or component being addressed by the Quality Agreement). This Part should note that the Quality Agreement is a living document and should describe the mechanism to ensure that the Quality Agreement and all of its attachments are current, especially specifications, contacts etc.

Note: All Parts below may include specific instructions on who to contact (e.g., quality assurance, regulatory affairs) in specific situations (e.g., Out of specification (OOS), recall). See Contact Matrix, Appendix B, for example contacts.

2. Compliance

This Part should:	<i>IPAC-RS Guideline Reference²</i>
[a] List all relevant regulations, standards, directives, and other documents to which supplier must comply (this should include at least reference to current versions of ISO 9001 and IPAC-RS GMP Guideline).	<i>5.2.3 Statutory and regulatory requirements</i> <i>7.2.3.2 Supply agreements and quality agreements</i>
[b] Address requirements regarding interactions with regulatory authorities . For example, notification regarding regulatory agency audits and audit reports/letters, processes for responding to audit reports/letters from regulatory authorities, and expectations regarding DMFs or other regulatory documents. Define if customer will be allowed on site during regulatory inspections and what input customer can have regarding responses to observations/findings.	<i>7.3.2 Design and development inputs</i> <i>7.3.2.1-7.3.2.5 Drug Master Files, Types of DMFs, Benefits, Requirements for DMF holders, Letters of Authorisation</i> <i>7.4.5 Use of DMFs</i>
[c] Note any requirements or restrictions regarding subcontracting . Should include whether subcontracting is allowed and describe the notification process, i.e., verbal or in writing, and whether prior approval is required. May also clarify party responsible for ensuring quality of subcontracted products	<i>7.2.3.2 Supply agreements and quality agreements</i> <i>7.4.1.1-7.4.1.3 Subcontracting, Control of supply chain, and</i>

² International Pharmaceutical Consortium on Regulation and Science (IPAC-RS) Good Manufacturing Practices Guideline for Suppliers of Components for Orally Inhaled and Nasal Drug Products. 2006.

and describe processes for ensuring such quality, including audits of subcontractors.	<p><i>Supplier qualification procedures</i></p> <p><i>7.4.3-7.4.4 Supplier data verification, Need for periodic requalification</i></p> <p><i>8.4 Analysis of data</i></p>
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3. Quality Assurance

This Part should:	<i>IPAC-RS Guideline Reference</i>
[a] Describe expectations that supplier have an adequate quality system to ensure that predetermined quality and compliance levels are maintained.	<p><i>4 Quality management system</i></p> <p><i>5 Management responsibility</i></p> <p><i>6 Resource management</i></p>
<p>[b] Describe intention of customer to conduct cGMP audits, and expectations regarding audits, e.g., frequency of audits, how long may they last, how much notice must be given; access to manufacturing, storage, laboratory facilities and all relevant documents; and agreed timeline for responses to audit observations. May include intention or plans for supplier self-inspections/audits. Note that <i>for cause</i> audits can be performed on a more frequent basis if justified.</p> <p>For n-1 suppliers: describe expectations of n-1 suppliers to conduct audits of n-2 suppliers. This may include requests to have access to manufacturing, warehousing and laboratory facilities. Define frequency and notice period for audits, and intentions to perform specific audits to resolve significant quality concerns. N-1 suppliers should have a supplier quality program and a system for managing n-2 suppliers (n-2).</p>	<p><i>7.3.1 Design and development planning</i></p> <p><i>7.3.2 Design and development input</i></p> <p><i>7.4.1.3 Supplier qualification</i></p> <p><i>7.4.1.1-7.4.1.3 Subcontracting, Control of supply chain, and Supplier qualification procedures</i></p> <p><i>7.4.3-7.4.4 Supplier data verification, Need for periodic requalification</i></p> <p><i>8.2.2 Internal audits</i></p> <p><i>8.5.1 Continual improvement</i></p>
[c] Describe expectations that suppliers have adequate qualified staff who are sufficiently trained to support the manufacture, testing and release of product.	<p><i>6.2 Human resources</i></p> <p><i>6.2.2 Competence, awareness and training</i></p>
[d] Describe the expectations regarding change control and notification processes. For example, a formal change control process is generally required, which would include identification, documentation (e.g., supporting data), notification procedure, appropriate review and approval of changes affecting products, processes, equipment, methods, and	<p><i>7.2.3.1 Change control and notification</i></p> <p><i>7.5.3 Component batch documentation</i></p>

<p>facilities. Specify the details of the change notification procedure, i.e., verbal or in writing, and note whether and when prior written approval is required. The quality agreement could include examples of changes subject to the formal change control process. The agreement may include a recommendation for the supplier to develop change control processes with <i>their</i> suppliers. Notification procedures for <i>unplanned</i> changes could also be included in this Part.</p>	
<p>[e] Describe responsibilities for deviations and investigations; provide examples of deviations (especially those requiring notification and investigation) and where such deviations are defined and agreed to between supplier and customer (e.g., in supplier standard operating procedures [SOP]); and define expected timelines and processes for analysis of deviations, investigations of OOS occurrences, and documentation and implementation of corrective and corrective and preventative actions (CAPAs).</p>	<p><i>8.3 Control of nonconforming product</i></p> <p><i>8.5.2 Corrective action</i></p> <p><i>8.5.3 Preventive action</i></p> <p><i>8.4 Analysis of data</i></p>
<p>[f] Describe expectations of each of the parties regarding timelines for reporting of potential recalls; roles and responsibilities of both parties in executing a recall and notifying authorities of recall. Describe clearly and precisely, which party has the authority to initiate a recall.</p>	<p><i>8.3 Control of nonconforming product</i></p> <p><i>8.5.2 Corrective action</i></p> <p><i>8.5.3 Preventive action</i></p>
<p>[g] Define responsibilities of each of the parties and describe expectations for tracking, documenting, storing and evaluating complaints related to component, raw materials, packaging materials, etc.; investigating and assessing complaint; processes for dispute resolutions; and providing final response. Clarify timelines for conducting investigations and providing investigation results. Timelines should fit with timelines in customer internal company SOP for complaints, e.g., if closure in 30 days is required, then response from the supplier is needed in 15 days.</p>	<p><i>7.2.3 Customer communication</i></p> <p><i>8.2.1.1 Complaints</i></p>
<p>[h] Define expectations for types of documentation to be provided to customer upon request, and timeline for provision of documentation; documents to be provided with manufactured/released and/or analyzed product batch. Define time period for document retention and any restrictions regarding destruction of documents. Describe any needs for special storage, security, or filing conditions. Note that documentation includes both paper and electronic formats.</p>	<p><i>4.2 Documentation requirements (and all subparts, especially 4.2.4 Control of records)</i></p>
<p>[i] Describe expectations for disposition of batch records. Define parties responsible for lot or batch approval and release. May include description of processes to ensure that non-conforming product is not released and is handled/disposed of appropriately and with permission of</p>	<p><i>7.2.2 Requirements related to the product</i></p> <p><i>7.2.3.3 Specifications</i></p> <p><i>7.5.3 Component batch</i></p>

<p>customer; and that any quality concerns with product are investigated and documented. May include expectations for sampling plans and expectations and timelines for retained samples.</p> <p>Requests for copies of completed batch records and other relevant documentation such as Certificate of Analysis or Certificate of Conformance for each batch may be included. Specific contents of these Certificates may be described (e.g., date of manufacture, test results, signatures). May stipulate authority in charge of final disposition of batch, approval and quality assurance process for shipping and receiving final batch, and requirements related to quarantined or rejected product.</p> <p>Describe care of the product during shipping and handling by n-1 or n-2 supplier to prevent, e.g., deterioration, theft, contamination. This may include requirements for specific packaging instructions and labeling.</p>	<p><i>documentation</i></p> <p><i>7.5.5 Preservation of product</i></p> <p><i>8.3 Control of nonconforming product</i></p>
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4. Starting Materials

This Part should:	<i>IPAC-RS Guideline Reference</i>
<p>[a] Describe terms of quality agreement regarding procurement of raw materials, e.g., resins. May include expectations for assuring raw materials supply, for timelines regarding notification of recalls from n-2 suppliers, and procedures for inspection of product and documentation upon receipt.</p>	<p><i>6.6 Suppliers and partnerships</i></p> <p><i>7.3.1.1 Design and development planning</i></p> <p><i>7.4.1 Purchasing process</i></p> <p><i>7.4.3 Verification of product</i></p> <p><i>7.5.3 Identification and traceability, Component batch documentation</i></p>
<p>[b] Describe general expectation for supply/quality agreements with n-2 suppliers.</p>	<p><i>6.6 Suppliers and partnerships</i></p> <p><i>7.2.3.2 Supply agreements and quality agreements</i></p>
<p>[c] Provide expectations for documenting physical and chemical properties such as identification/grade, mechanical properties, certification, any compendial testing results, and requirements regarding testing for monitoring for transmissible spongiform encephalopathies (TSEs) and ensuring protection from TSE contamination.</p>	<p><i>7.2.3.3 Specifications</i></p> <p><i>7.3.1.1 Design and development planning</i></p> <p><i>7.3.1.2 Component and material use-by/requalification dating</i></p>

[d] Describe requirements for sampling and testing in-coming raw materials. May include requirements for retaining samples of raw materials and meeting specifications. Testing and specifications may include extractables and residues.	<i>7.3.1.2 Component and material use-by/requalification dating</i>
[e] Describe expectations regarding proper storage of raw materials to ensure quality.	<i>7.3.1.2 Component and material use-by/requalification dating</i>

5. Manufacturing

This Part should:	<i>IPAC-RS Guideline Reference</i>
[a] Describe requirements for process and equipment validation and qualification . Requirements may include equipment used for manufacturing and packaging. Timelines for reporting, to the customer, out of validation/qualification equipment may be stipulated.	<i>4.2.3 Control of electronic documents</i> <i>6.3 Infrastructure</i> <i>7.1 Planning of product realization</i> <i>7.1.3.3 Product and process validation and changes</i> <i>7.3 Design and development</i> <i>7.3.6 Design and development validation</i> <i>7.5.2 Validation of process</i> <i>7.6 Control of monitoring and measuring devices</i> <i>7.3 Design and development</i> <i>7.5.1 Control of production</i> <i>7.5.2 Validation of process for production and service</i> <i>9.1 Facilities, equipment and operating conditions</i>
[b] Describe requirements for manufacturing environment and expectations for cleanliness and hygiene . For example, this Part may require that facilities have been cGMP audited by customer. May include requirements for e.g., dedicated facilities and equipment, requirements for segregation from specific types of products, and line clearance. This Part may	<i>6.3 Infrastructure</i> <i>6.4 Work environment</i> <i>9.1.3 Equipment and maintenance</i>

<p>address, expectations for cleanrooms, pest control, microbial control, cleaning and cleaning validation, cleaning agents, mold release agents (if allowed), foreign particles issues, etc. Manufacturing sites may also be specified.</p>	<p><i>9.1.4 Cleaning (and all subparts: Cleaning validation, Re-useable bulk storage containers, Material changeover)</i></p> <p><i>9.1.5-9.1.11 Pest control, materials, line clearance, segregation, overruns, waste material, personal hygiene</i></p> <p><i>9.2.1-9.2.3 Environmental conditions and cleanrooms</i></p> <p><i>9.2 Component cleaning</i></p> <p><i>9.3 Foreign particles</i></p>
<p>[c] Describe expectations for amount of retained samples and period of retention.</p>	<p><i>7.5.4 Customer property</i></p> <p><i>8.2.1.1 Complaints</i></p> <p><i>8.2.4.1 Characterisation and functionality testing of OINDP components</i></p> <p><i>8.3 Control of non-conforming product</i></p>
<p>[d] Clarify if reworking/reprocessing is allowed, including re-grinding.</p>	<p><i>7.1 Product realization</i></p> <p><i>8.3 Control of non-conforming product</i></p>
<p>[e] Describe requirements for storage of product.</p>	<p><i>7.5.5 Preservation of product</i></p> <p><i>7.3.1.2 Component and material use-by/requalification dating</i></p> <p><i>8.2.4.1 Characterisation and functionality testing of OINDP components</i></p>

6. Testing

<p>This Part should:</p>	<p><i>IPAC-RS Guideline Reference</i></p>
<p>[a] Describe expectations for lab methods for testing. For example, may include expectations that methods be included in change control procedures; may describe requirements for any</p>	<p><i>7.3.1.1 Design and development planning</i></p>

<p>method transfers, documentation, and verification of testing results. May describe specific tests to be performed, e.g., controlled extraction studies.</p>	<p><i>8.2.4 Monitoring and measurement of product</i></p> <p><i>8.2.4.1-8.2.4.4 Characterisation and functionality testing of OINDP components, Control of ancillary materials, Controlled extraction studies, Control of extractables</i></p>
<p>[b] Describe procedures to be followed in case of an Out-Of-Specification (OOS) result. For example, this may include requests for notification of a confirmed OOS within 1 day due to the requirement to issue field alerts within 3 days; and clarification of when and if the customer has the right to approve (“sign-off” on) the OOS.</p>	<p><i>8.3 Control of non-conforming product</i></p>
<p>[c] Explain requirements for qualification and validation of lab instruments and methods.</p>	<p><i>4.2.3 Control of electronic documents</i></p> <p><i>7.1 Planning of product realization</i></p> <p><i>7.3.1.1 Design and development planning</i></p> <p><i>7.3.1.2 Component and material use-by/requalification dating</i></p> <p><i>7.6 Control of monitoring and measuring devices</i></p> <p><i>8.2.4 Monitoring and measurement of product</i></p> <p><i>9.1 Facilities equipment and operating conditions</i></p>
<p>[d] Describe expectations regarding lab environment.</p>	<p><i>6.3 Infrastructure</i></p> <p><i>6.4 Work environment</i></p> <p><i>9.1 Facilities equipment and operating conditions</i></p> <p><i>May include:</i></p> <p><i>9.1.1-9.1.3 General, Facilities design, Equipment and maintenance</i></p> <p><i>9.1.5 Pest control</i></p>

	<i>9.1.11 Personal hygiene</i>
[e] Define parties responsible for component stability studies or shelf-life justification . Describe requirements for stability studies such as length and conditions. Include, for example, requirements for storage containers and conditions.	<i>7.3.1.2 Component and material use-by/requalification dating</i>

7. Specifications

This Part should:	<i>IPAC-RS Guideline Reference</i>
Describe relevant quality aspects of the “product,” e.g., name, dimensions and limits, specifics of raw material used, cleanliness standards, test methods, acceptance criteria. Define party responsible for determining and changing any specifications, including notification of such changes. A full description of the product specifications can be attached as an appendix.	<i>7.2.3.3 Specifications</i>

8. Responsibility Matrix

This Part should:	<i>IPAC-RS Guideline Reference</i>
Include a responsibility matrix as an appendix or attachment. This matrix should provide a clear summary of roles/responsibilities of each of the parties involved in the relationship. (see Appendix A, below, for example)	<i>4 Quality management systems</i> <i>4.1.1-4.1.3 Quality unit, Quality unit authority, Quality unit responsibility</i> <i>5 Management responsibility</i> <i>5.1 Management commitment</i> <i>5.2 Customer focus</i> <i>5.5 Responsibility, authority and communication</i> <i>6.2.2 Competence, awareness, and training</i> <i>7.2.3.2 Supply agreements and quality agreements (Includes example of responsibility matrix)</i>

9. Confidentiality and Restriction of Use

This Part should:	<i>IPAC-RS Guideline Reference</i>
Describe requirements for protection of confidential information shared between parties.	<i>7.2.3.2 Supply agreements and quality agreements</i>

10. Health and Safety

This Part should:	<i>IPAC-RS Guideline Reference</i>
Include expectations for operating within current health, safety and environment legislation applicable at sites manufacturing the product.	<i>5.1 Management commitment</i> <i>5.2.3 Statutory and regulatory requirements</i>

11. Definitions

This Part should:	<i>IPAC-RS Guideline Reference</i>
Provide relevant definitions of specific terms important for clear understanding of agreement, e.g., technical, product, quality terms.	<i>1 List of compounds to be addressed (Table 1)</i> <i>3.0 Terms and definitions</i>

Appendix A

Example of a Responsibility Matrix

RESPONSIBILITIES	Supplier	Customer
1. Analytical, Laboratory, Sampling & Control		
Specifications and test instructions for raw materials, packaging materials, in-process controls, and products	✓	Review and approval, approval of amendments
Sampling, analysis and release of Raw Materials and Packaging Materials	✓	
In-process analyses for Manufacture	✓	
Sampling and analysis of packaging materials	✓	Only where legally required
Retaining and storing of samples of all Raw Materials	✓	
Reference standards for laboratory analysis	✓	For analyses at customer only
2. Quality Assurance Activities		
Approval of master batch documents	✓	Review and acceptance, approval of amendments
Release of Product for shipment to customer	✓	
Batch number allocation for Product	✓	
Qualification of any subcontract facilities	✓	
Approval of any subcontract facilities	✓	✓
Assurance of correct storage conditions for Products prior to shipment to customer	✓	
Preparation and review of the Product batch record	✓	
Manufacturing & testing records and associated documents	Original retained	Receive copy as defined
Certificate of Analysis & Certificate of Compliance	✓	Receive copy
Archiving of raw data (manufacturing, testing)	✓	
Qualification (specifications, GMP, audits, applicable regulations) for material, component, packaging supplier	✓	
Responsible for failure investigation in case of batch failure to Product stage	✓	
Responsible for failure investigation in case of batch failure from receipt of Product	✓	✓

Change Control	Initiate Approval	Approval
Shipping documentation	✓	
Hazard data sheet provision	✓	✓
Annual Product Review on Product manufacture	✓	
3. Regulatory Documentation		
Supply of all necessary technical and regulatory documentation related to activities performed by customer	✓	
Chemical Manufacturing and Control information	Input and data provision and submission (DMF)	Review and submission (if applicable)
Plant registration licenses	✓	
4. Raw Materials and Packaging Materials		
Raw Material and Packaging Material supplier qualification	✓	
Quality follow-up for Raw Materials and Packaging Materials purchased for customer	✓	
Approval of Raw Material and Packaging Material process and change control	✓	✓
5. Validation		
Validation of Manufacturing process (including cleaning validation)	✓	
Validation of test methods	✓	
Transport validation studies	✓	
Qualification of all equipment for Manufacturing and associated analysis	✓	
6. Complaint Handling, Drug Safety		
Review and answering of Product quality complaints	Investigation where relevant	Database and report
Review and answering of medical complaints	Investigation where relevant	Database and report
Decisions regarding recalls and field corrections and alerts	✓	✓

Appendix B

Example of a Contact Matrix

Contacts and Responsible Persons

<u>Contract Giver:</u>	<u>Name:</u>	<u>Fax:</u>	<u>Phone:</u>
Pharmaceutical Matters:			
Deputy:			
Head of Quality Assurance:			
Deputy:			
Batch Release Officer			
Production Manager:			
Deputy:			
Quality Control Manager:			
Deputy:			
Responsible Lab Head:			
Other Contacts:			
Logistics Manager			
Regulatory Affairs			

<u>Contract Acceptor:</u>	<u>Name:</u>	<u>Phone:</u>	<u>Fax:</u>
Pharmaceutical Matters:			
Deputy:			
Head of Quality Assurance:			
Deputy:			
Production Manager:			
Deputy:			
Quality Control Manager:			
Deputy:			
Other Contacts:			
Packaging			
Regulatory Affairs			