An International Pharmaceutical Supply Chain Consortium

APRIL 2018

RX-360 BEST PRACTICES QUALITY AGREEMENT GUIDE

VERSION 2.0

Scope

Structure

Framing Content

Technical Content

Negotiate

Review

Signature

Maintain

Contents

Introduction

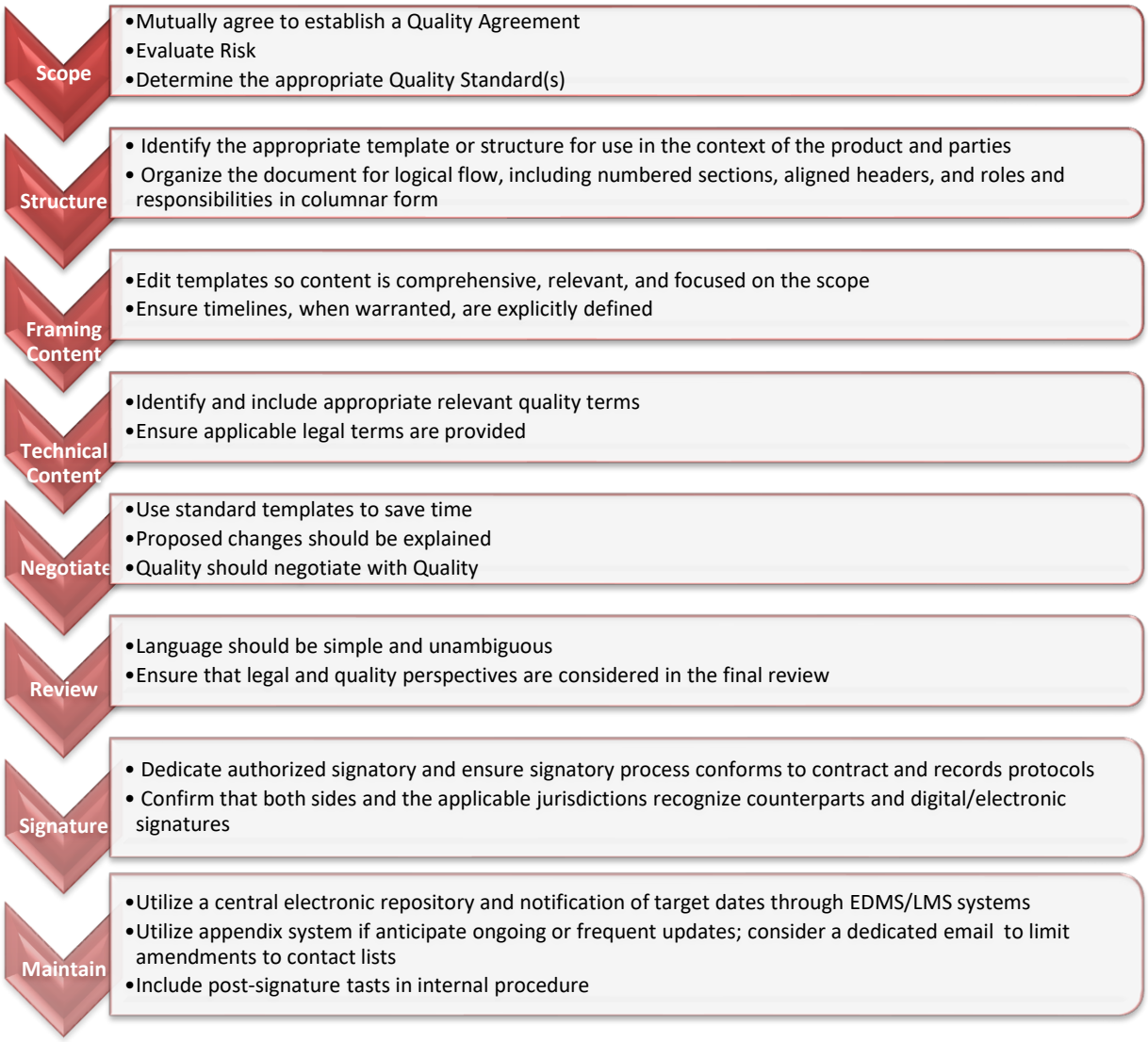

Fig. 1. The Quality Agreement Process as outlined in this guide.

This Best Practices Quality Agreement Guide is intended to assist both Customers and Suppliers in efficiently managing the initiation, negotiation, implementation, and ongoing maintenance of quality agreements. "Supplier" is used broadly in this document to refer to a company that provides materials, products, or services. Establishing a quality agreement can be time-consuming as negotiations, misunderstandings, and inflexibility frequently cause delays in the process.

This guide contains some best practices, sample language, external references and resources, along with solutions to routine issues that come up during the quality agreement process. Perspective from both suppliers and manufacturers, presents a balanced view designed to

assist both parties in achieving a complete, concise agreement. Flexibility and compromise are needed in order to understand and work together to meet the requirements of both parties.

Using this Guide

The sections are present in the process flow (see above) of implementing a Quality Agreement. Throughout this document, **Best Practices and Tips** are outlined in a red box with appendices offering a set of comprehensive tools to aid in developing a quality agreement program including:

- Content Regulatory References
- Sample Content Selection Matrix
- List of Industry Templates and Guides

The objective of the Supplier Led Working Group is for this guide to help facilitate a more efficient and effective quality agreement negotiation process. As with all of our other documents we have published, this document will be reviewed and updated based on the most current industry and regulatory practices.

We welcome any questions or comments you may have on the material in this document.

Rx-360 Supplier Working Group Co-Chairs:
Rick Calabrese, Sartorius-Stedim rick.calabrese@sartorius-stedim.com
Gary Perkins, Millipore Sigma gary.perkins@sial.com

Scoping Quality Agreements

A Quality Agreement is a legally binding agreement intended to define quality unit roles, responsibilities, relationship, requirements and commitments of the Purchaser/Customer (hereafter Customer) and of the Supplier or Sponsor (hereafter Supplier).

It establishes mutual understanding between the two parties involved in the activity.

When determining whether a quality agreement is necessary, consider the applicable law and regulations for the product or services and the use thereof. Where the law mandates quality requirements, as under EU GMP or requires a Quality Agreement, there should be no question from either party that a Quality Agreement is needed.

Where the law and regulatory requirements are not as clear, a risk assessment can be performed to determine whether a Quality Agreement is required. The risk assessment should evaluate the criticality of the material or service and impact on the final product. For products that have some industry standard quality requirements, such as those falling under the United States of America Food and Drug Administration Code of Federal Regulations Title 21-Food and Drugs, or PIC/S GMP Guides and International Pharmaceutical Excipients Council (IPEC) Guidelines, the risk assessment will likely weigh toward establishing a Quality Agreement to comply with those quality requirements.

Some categories of materials/products are not regulated or the legal requirements or industry standards/guidelines differ from the Customer's requirements Before defining requirements, understand the quality system that governs the manufacture/supply of these materials and conduct a risk assessment. Particularly for products/services with potential risk, a Quality Agreement is useful in providing both parties with clear expectations and a commitment to quality standards.

In all cases, the agreement should be tailored to capture the specific customer requirements, necessary for the function of the material or service and the relevant industry standards to which the materials (or service) are produced and supplied under. This will create efficiency over sending a template with irrelevant sections or an improper scope.

It is recommended that the scope of the Quality Agreement should cover the following sections

- Purpose and scope to specify the relationship between the two or more parties
- Product(s)/service(s) covered under the agreement
- Terms of the agreement
- Responsibilities of each party related to quality activities
- Communication mechanism and contacts

The following quality agreements templates and guidelines exist within the industry and are useful references when working with a specialized quality agreement. Before relying on an industry temple/guideline, companies should ensure they are using the most current version. Most are "living documents" and updated regularly.

- For Excipients: IPEC's "The IPEC Quality Agreement Guide and Template" (2017)
  - IPEC Quality Agreement Guide and Template
- For APIs: Active Pharmaceutical Ingredients Committee's "Quality Agreement Guideline & Templates APIC" Version 02 (July 2017)
  - APIC Quality Agreement Template
- For Single-use Biopharmaceutical manufacturing products: Bio-Process Systems Alliance's "Consensus Quality Agreement Template" (2014)
  - BPSA Consensus Quality Agreement Template

Best Practices for Scoping:

- Establish initial communication between parties to agree upon the need for a Quality Agreement and the scope.
- Where Quality Agreement is not legally mandated, establish risk assessment to base agreement on criticality.
- Scope the agreement for the products, applicable regulatory requirements and Supplier standards.
- Leverage accepted industry templates where applicable to increase efficiency.

Managing Multiple Sites/Parties

Quality Agreements can be difficult to manage between two parties, let alone when multiple parties and sites are involved. When there are multiple sites or parties included in a Quality Agreement, there are a few things that can be done to minimize confusion and help ensure the agreement process goes smoothly, and the final agreement is robust and usable for all sites or parties.

Multi-Site Agreements

Multiple sites may need to be included to cover numerous supplier products that have different manufacturing and packaging locations, or for multiple customer use sites and purchasing sites. In these cases, information needs to be clearly separated by site or by product.

1. Use Matrix tables to better organize and present complex multi-site details

The use of appendices and matrix tables helps make this information clear and concise and is highly recommended. Here are some examples where a matrix table as an appendix can be used to clearly present information from multiple sites.

Appendix Examples

- Contact List (for each supplier-site and end-user site)
- Product or Part Numbers (for each supplier-site, and end-user site)
- Product Quality Level (API, Excipient, Med Device, Reagent, etc.)
- Manufacturing or Packaging Site Addresses
- Responsibilities of Parties

By including specific product quality levels and site locations in the product table, the use of appendices can be used to capture and control many of the dynamic details of the quality agreement. This allows easy changes to an appendix whenever a contact name changes, products need to be added or deleted, or when additional manufacturing locations are added or deleted to the scope of the agreement. The main body of the agreement can have language that allows for changes to an appendix without having to re-review the entire agreement. The appendix change can be reviewed, and signed by each party, and replaced with an effective date. This allows for much more efficient process that keeps the agreement more up to date because all parties aren't "avoiding" the arduous process of changing the main agreement.

2. Use a Pre-Approved Deliverables sheet to avoid Signatures Across Multiple Sites

When multiple manufacturing sites from one company are represented in an agreement, the most efficient situation is to have one signatory sign for all sites. This is usually difficult because all sites want/need to make sure that they can meet the requirements of the agreement. One potential solution for this is the use of an internal "Pre-Approved Deliverables" document.

Quality Agreement Multi-Site Pre-Approved Elements

The following items have been agreed upon as acceptable elements across sites AA, BB, CC, and DD and can be incorporated into future quality agreements without need for site approval.

Element Type	Quality Agreement Elements
Complaints	If CUSTOMER discovers nonconformity after delivery, CLIENT will complete the investigation within 30 days, otherwise provide an interim report at 30 days. If CLIENT agrees with nonconformity, CAPA plan will be sent to CUSTOMER within 10 days.
Delivery	Shipment of material between CLIENT and CUSTOMER must include temptales
Development	CLIENT will generate manufacturing records for product and submit them to CUSTOMER for approval prior to use and prior to any changes.
Development	CLIENT will generate SOPs for product specific analytical methods and submit them to CUSTOMER for approval prior to use and prior to any changes.
Documentation	CoA, CoO, and CoC provided upon batch release by CLIENT QA
Documentation	Copies of completed batch record and analytical test data provided by CLIENT Project Management
Documentation	CLIENT will provide requested information for any product complaints or regulatory requests within two business days.
Documentation	CLIENT will retain batch record documentation for no less than 10 years or for the duration of the Master Agreement.
Documentation	Copies of Regulatory inspection reports and CLIENT responses will be sent within 1 business days of responses being sent to the Regulatory Agency for inspections that directly relates to the CUSTOMERs product.
Notification	Notification within 3 business days of significant nonconformances or confirmed OOS during product manufacturing or testing
Notification	Notification within 3 business days of any change to any raw material supplier
Notification	Notification within 3 business days of significant nonconformances discovered after product delivery.
Notification	Notification within 1 business day of an inspection by any Regulatory Agency that directly relates to the customers product.
Notification	Notification within 10 business day of receipt of an inspection report by a Regulatory Agency that directly relates to the customers product.
Retention	Maintain enough retention samples for 2X testing for 1 year past shelf life
Testing	Testing will be completed not more than 30 days from the date of manufacture
Validation	If contracted, CLIENT will generate Method Validation Protocols for product and submit them to CUSTOMER for approval prior to use and prior to any changes.
Validation	If contracted, CLIENT will generate Stability Protocols for product and submit them to CUSTOMER for approval prior to use and prior to any changes.
Validation	If required, CLIENT will generate Process Validation Protocols for product and submit them to CUSTOMER for approval prior to use and prior to any changes.
Quality System	CLIENT will follow and maintain ICH Q7 compliant systems

Fig. 2. Sample of pre-approved deliverable sheet used to assist negotiations.

The use of a deliverable sheet has a number of benefits, among them:

- Common pre-approved deliverables are collected for multiple sites into one document.

- One designated signatory can sign for multiple sites if all pre-approved elements are met and it aligns with applicable internal governance company standards as to who can sign company agreements.
- If all elements cannot be met, only those items in the gap need to be reviewed by each site, not the entire document.

This summary document boils down the range of deliverables for most common elements within a quality agreement so that the main signatory already knows what is acceptable/agreeable for each site the document represents. By using this pre-completed document when negotiating the notification dates, deliverables, and other actionable items within an agreement, the signatory already knows whether all their sites can comply with the finished document. If all deliverable elements fall within the ranges of the Pre-Approved Deliverables sheet, then one signatory can sign for all sites without the need for sending for multiple reviews. This "Pre-Approved Deliverables" document would be for internal use only and would not need to be shared with the other party in the agreement negotiation.

In the event that some elements are outside the pre-approved document, and the sites need to review deliverable commitments, the most efficient options would be for the sites to review only the gap element and give consent or disapproval to the coordinator that is negotiating and signing the final document. By avoiding review of the entire document and avoiding collection of signatures from every site, you can save weeks or months from the approval process.

If all sites are required to sign the agreement, try to use the Pre-Approved Deliverables document as a guide and only require the review of the elements that fall outside of the agreed upon ranges. Even though all sites must sign, streamlining the review can make the process much faster than doing a full review of the document at every impacted site (which also can open up the document to multiple interpretations which can mire the process in even more questions and follow-ups).

Best Practices for Multi-Site Agreements:

- Use Appendix matrix tables to display products, sites, contacts, etc.
- Allow Appendix information to be updated without having to re-approve the entire agreement.
- Use Pre-Approved Element tables to avoid additional review at each site.

Multi-Party Agreements

Multi-party agreements include many different contractors that might be involved in the entire product manufacturing chain. Examples of these various types of roles are:

- Sponsor or Customer
- Contract Manufacturer
- Fill-Finish Contractor
- Contract Test Lab
- Contract Warehouse
- Distributor

Agreements among these multiple parties (more than 2) can be very difficult because of the added possibility for miscommunication and the common misunderstanding of the role of each party entering into the agreement.

1. Try to avoid entering into multi-party agreements when possible.

Establishing individual agreements with different contractors provides a level of control that minimizes confusion, miscommunication, and potential for handoff issues and finger-pointing. An agreement with each individual party allows more clearly established responsibilities. Examples of this common setup are:

Sponsor ↔ Contract Manufacturer 1
Sponsor ↔ Contract Manufacturer 2
Sponsor ↔ Fill-Finish Contractor
Sponsor ↔ Contract Test Lab
Sponsor ↔ Distributor

Another possible option to avoid multi-party agreements, is to provide a generic quality statement to relevant third parties. The quality statement covers a subset of the most important responsibilities (e.g. level of cGMP applicable). It can be issued once and then distributed to a larger number of third parties. A template is already available, that covers the quality relationship between Sponsor/Customer ↔ Distributor ↔ Manufacturer (refer to IPEC's "The IPEC Quality Agreement Guide and Template" (2017)).

2. Establish a joint kick-off conference call or face to face meeting with ALL parties to begin the agreement process

There are times when it is not practical or possible to have individual agreements with each contractor. In these scenarios, the best practice is to start the agreement process with a joint conference or meeting with all parties to the agreement. The specific agenda of this kick-off call is to define the relationships and the goal of the agreement. With a constructive dialogue,

the companies can be open-minded about which is the best agreement template to start with and proceed from there. The key to success is to keep lines of communication open and engage in face-to-face or phone discussions to resolve questions rather than relying on email. This will rapidly accelerate understanding and completion among multiple-parties.

a. Define the role of each party in the relationship
b. Have a kickoff conversation with all of the company coordinators to discuss the best template to begin with before starting negotiations. (example: conference call or face to face when practical) Be open minded and pragmatic.
c. Apply Multi-Site best practices such as responsibility matrices and tabled appendices to organize and review information.
d. Touch base often to work out any miscommunications
e. Follow up meetings, conference calls with a summary, including accepted roles, action items and commitments.

Communication is key to the success of multi-party agreements. Email can be used to answer a quick question, but plan ahead to have routine conference calls to follow-up on progress and to settle misunderstandings or disagreements. Quality Agreements can sit on someone's desk for weeks or months at a time and when they are looked at again, some understanding or progress may have been lost. Routine meetings with follow up summary, keep all parties on track and engaged.

Best Practices for Multi-Party Agreements:

- Avoid entering into multi-party agreements when possible.
- Facilitate a joint kick-off meeting with all parties to the agreement.
- Agree up front on roles, relationships, goal of the agreement and best starting template.
- Apply Multi-Site best practices.
- Schedule routine progress meetings and touch base often by phone with all parties to keep on-track.
- Keeping and distributing summary notes after meetings.

Format & Structure

A stand-alone document, separate from any associated supply agreement(s) avoids providing regulatory agencies with unnecessary business information. From a legal standpoint, a self-contained contract limits the complexity and simplifies the process for revisions and updates.

Common formats used to draft a quality agreement are legal-style (sections laid out in paragraph form) or a combination of legal-style with the roles & responsibilities presented in tabular fashion. Displaying the critical or actionable elements in a numbered, columnar view aids in the rapid review and assessment of the presented information. A table that continues past the page break should begin with the column headers, or a repeating header row, as shown in the example below.

	RESPONSIBILITIES	SUPPLIER	CUSTOMER
1	**Compliance**		
1.1	*Conform to the WHO Guideline Good Trade and Distribution Practices for Pharmaceutical Starting Materials and other quality criteria defined in the scope of this agreement*	✓	
1.2	*SUPPLIER shall have a Quality Agreement(s) with the original manufacturer and/or any third parties used for production, packaging, warehousing, testing or processing the PRODUCT in any manner that could be viewed during an audit of SUPPLIER.*	✓	
1.3	*Mutually agreed upon specifications for the PRODUCT which are the subject of this agreement.*	✓	✓
1.4	*Changes to the agreed upon specifications must be mutually agreed upon and communicated in writing between the parties to this agreement, except for compendial changes which can be implemented without mutual agreement. Compendial changes must be implemented by the compendial implementation date.*	✓	✓
1.5	*Ensure that the specifications for compendial PRODUCTS are in compliance with the current compendia.*	✓	
1.6	*Supply PRODUCTS that conform to the mutually agreed upon specifications.*	✓	
2	**Labelling**		
2.1	*Agree upon special labelling requirements, as applicable.*	✓	✓
2.2	*Original labelling from manufacturing site being visible.*	✓	
	RESPONSIBILITIES	**SUPPLIER**	**CUSTOMER**
3	**Storage and Distribution**		
3.1	*Ensure that PRODUCTS are stored and shipped in accordance with manufacturer's recommended storage conditions.*	✓	
3.2	*Ensure that during storage and shipping of PRODUCT, all reasonable care is taken to avoid contamination or mix up*	✓	
3.3	*Assurance of correct storage conditions for PRODUCT prior to shipment to Customer*	✓	
3.4	*Approval to ship PRODUCT to Customer*	✓	
4	**Deviations**		
4.1	*Investigate and record deviation in SUPPLIER perimeter.*	✓	
4.2	*Transfer of all information coming from manufacturer*	✓	
5	**Change control**		
5.1	*Evaluate and communicate any change related to the distribution flow of PRODUCT or that may an impact on the quality of the PRODUCT, based on agreed criteria and timelines,.*	✓	
5.2	*Transfer all information coming from manufacturer*	✓	
6	**Transfer of information**		
6.1	*Inform CUSTOMER about all quality or regulatory PRODUCT related information received from manufacturer.*	✓	
6.2	*Inform manufacturer about all quality or regulatory PRODUCT related information received from CUSTOMER.*	✓	
7	**Complaints**		

Fig. 3. Example of Quality Responsibilities in columnar format

The structure or arrangement of the elements within a Quality Agreement can support the review and revision process by the participating parties. Following a logical flow, from the introduction of parties through scope and responsibilities to the signatures, allows the reviewers to assess the applicability of each section and accept or redline/negotiate.

Confining topics or similar topics to consecutive, numbered sections reduces the reviewing time and decreases the likelihood of duplicate clauses being overlooked, leading to conflicts or confusion regarding expectations and requirements.

Best Practices for Structure:

- Construct the Quality Agreement as a stand-alone document.
- Consider presenting the roles & responsibilities for both parties in columnar format.
- Organize the document to facilitate a logical flow of section/clauses, including numbered sections and aligned headers.

Content

Content Generally

The content of a quality agreement is contingent on the type of supply (e.g. Active Pharmaceutical Ingredients, Excipients, Components, Single-use products for manufacturing, Ancillary materials, Bulk Product, Finished Product, Medical Devices, etc.) or service (e.g. Contract Laboratories, Warehousing, Carriers, etc.) and the scope of the agreement.

When crafting a quality agreement, the contracting parties should ensure that the content is comprehensive, relevant and focused. Only those topics applicable to the contract should be addressed. For instance, it may be unnecessary to address Finished Product stability in a quality agreement concerning supply of Active Pharmaceutical Ingredients. Rather, the unnecessary content may act only to distract and lend confusion to the scope.

On the other hand, quality agreements with Supplier/Service providers that differ in nature may contain similar topics. Notwithstanding, it is important to acknowledge that even when similar topics are addressed, the terms and conditions contained therein may have subtle or even substantial differences. For instance, the change control section for Finished Product supply may contain a term addressing the management of the regulatory file/dossier; however, such a term would not be contained in a quality agreement for transportation services. Contracting parties should also be mindful that the content of a quality agreement may vary depending on the governing regulations of the applicable regulatory jurisdiction, as applicable.

If quality agreement templates are used, particular attention should be made to select an appropriate template for the type of supply/service. For example, a quality agreement template specific for the supply of Excipients should not be arbitrarily used for negotiations of ancillary materials such as filters. If templates are to be used, the contracting parties should be open to adding, deleting or modify the content of the template to be comprehensive, relevant and focused for the type of supply/service.

QUALITY AGREEMENT FRAMEWORK

There are specific terms that should be outlined to describe the framework for the agreement. Typically found in the preamble/recitals of the agreement, such basic content may include:

I. Scope of the agreement
II. Required licences
III. Governing Regulations / Guidance's / Standards

I. Scope

The scope of the quality agreement should align with the supply or services rendered and will delineate the boundaries of the relationship that the agreement is meant to cover. This protects the parties from the potential argument that the agreement could cover more products, or more activities, than what was intended. Once the scope of the agreement is clear and understood, the quality agreement will act to comprehensively set-forth the obligations and responsibilities of the parties within the agreed boundaries.

II. Required Licences

The required licenses, permits and approvals to carry out the business may vary by jurisdiction. Regardless of the number or type of licenses, permits, and approvals, the parties to the agreement should confirm that they are in a position to hold and will maintain the required licenses, permits and approvals to fulfil their obligations for the term of the agreement. As well, any revocation, cancellation or expiry of any licence, permit or approval necessary to perform the services under the scope of the agreement should be communicated to the other party without delay. Some companies may elect to exclude such a term in the quality agreement if covered under the commercial agreement.

III. Governing Regulations / Guidances / Standards

Quality agreements are not intended to repeat the laws, regulations, industry guidances or standards; the purpose of a quality agreement is to assign the respective quality roles and responsibilities as they relate to the relationship of the parties. However, the quality agreement should outline the governing regulations, guidances, or standards under which the agreement is made such that the parties agree which quality responsibilities need to be assigned. Furthermore, for some types of quality agreements, the regulatory authorities may expect such a written commitment. According to FDA's draft "Guidance for industry Contract Manufacturing Arrangements for Drugs: Quality agreements" FDA expects that Quality agreements will specify that services provided by the Contracted Facilities (including contract laboratories) will comply with cGMPs and the applicable local (state and national) authorities as agreed by the parties."

For unregulated suppliers, where regulations, guidances or standards do not apply, supplier internal quality systems should be in place and followed.

STANDARD LEGAL TERMS

Regardless of the type of supply/service in scope, quality agreements are drafted as legally binding documents. Barring any language to the contrary (such as, "this document is not intended to legally bind the parties but to serve as a guide…"), the document generally becomes binding when both parties reach formal agreement. Although the agreement can

be verbal, the signatures of both parties give effect to the agreement.[1] Technically speaking, no additional terms are necessary to create a 'legal document.' However, to create a clearer agreement and protect both parties against potential disputes consideration should be made to include the following legal terms, at a minimum:

I. The Parties
II. Term (effective date/termination/renewal)
III. Amendments
IV. Assignment
V. Other Agreements/Precedence
VI. Confidentiality
VII. Severability
VIII. Governing Law & Jurisdiction
IX. Counterparts

When drafting, parties should be aware that standard legal terms may vary in scope or interpretation by jurisdiction. When drafting Agreements between parties from different jurisdictions, additional care should be taken to clearly state terms and expectations. For complex Agreements, cross-jurisdictional Agreements, or those where a language barrier becomes an issue, consulting with local counsel is often advised.

I. The Parties

The parties to any quality agreement identify the companies or legal entities responsible for the quality commitments made in the Quality Agreement and signing the agreement. By extension, these are the parties who will bear the responsibility for managing future contract resolutions or disputes. The parties should be identified by the name under which each entity is incorporated or organized and an address at which it can be contacted. It is also common to indicate the state or jurisdiction in which the entities are formally incorporated. Depending on the nature of the agreement, the parties may also include affiliate companies or locations. In cases where the party that supplies a product and the sites involved in the manufacture of the product are affiliated, but different legal entities, additional language is needed to clarify that each reference to Supplier shall be interpreted as a reference to Supplier and/or the affiliated manufacturing entity, as applicable. For further discussions regarding quality agreements that encompass more than two parties, see the Managing Multiple Sites/Parties Section.

NOTE: It should be verified between the Parties that any location listed as a Party to the Agreement is a Legal Entity with signature authority according to the companies' own bylaws and/or relevant policies. It is not necessarily true that all locations for a company can enter into a legally binding contract or agreement.

[1] For more information on the legality of signatures and electronic signatures, please see the discussion in the Signing and Maintaining Agreements Section.

II. Term (effective date/termination/renewal)

The term of the quality agreement refers to the time, generally dictated in years, during which the Agreement is considered effective. Company experience and policy will likely dictate the standard term(s) for quality agreements. Generally, the terms of Quality Agreements follow one of three options:

1) A flat chronological term, usually stated in years (i.e., "This Agreement shall remain in effect for five (5) calendar years from effective date.") A flat term is the most straightforward, but may require further amendments as the agreement ages.
2) A term dependent on a "trigger" event, such as the life of the product or manufacture of a particular element. This may eliminate the need for multiple amendments or continuous renewal, but it should be considered whether or not the products or services provided may need to have changes over the life of the contract. Some companies are reluctant to use such terms in the quality agreement as they create uncertainty regarding the chronological scope and may extend the requirements of the agreement indefinitely. If using a triggered term, recommended best practice is to include a renewal or review provision with a fairly short term to ensure the agreement reflects current production practices.
3) Many agreements utilize a conservative flat term coupled with an "evergreen" or renewal provision to allow the agreement to continue past the set term without formal amendment. Most renewal provisions trigger automatically unless either party to the agreement takes a specified action (such as providing notice to amend or terminate before a certain date).

The term section may also have language detailing the rights of the Parties to terminate the contract upon breach or for mutual convenience. This may be as simple as a short time frame for notice, or it may include a longer time frame with additional promises and protections (e.g. continued rights to purchase inventory for a period). Most rights to terminate will require that the terminating party provide notice, generally in written form, to the other party. In many agreements a clear breach of the agreement not corrected in a timely fashion provides ground for termination without notice. If there are obligations that should last beyond termination of the agreement (common terms include confidentiality requirements, record retention, or audit obligations), these should be explicitly noted as surviving the base contract and specific terms provided.

The Effective Date of the Agreement shall also be defined. Date of last signature is a common approach, but in some cases, the date for a quality agreement may need to be linked to another document. For example, if the quality agreement is being signed in connection with a Master Supply Agreement / Master Services Agreement ("**MSA**"), the effective date for the MSA may take precedence and then would be mentioned via reference in the quality

agreement. There may be other accompanying documents that contain certain elements of the quality agreement that accompany it, such as a supply agreement or MSA. It should be ensured there is not a conflict in terminology or requirements between the other governing documents and is generally preferable to specify the effective date in the agreement for the sake of clarity.

III. Amendments

When applicable, a process for amending a quality agreement should be outlined as part of the agreement. Given the extensive time involved in drafting, finalizing, and signing a quality agreement, it is often efficient to provide a short-form amendment process to add or delete products or services in addition to a formal process to amend the content of the agreement clauses. The amendment process can take several forms:

- A short list/appendix of products or services to be added (or deleted)
- Complete revision of the Product or Service list
- Other types of amendments, where the content of the agreement clauses are being adjusted

An amendment process should require that changes to the original quality agreement be mutually agreed upon and set out in writing to avoid unilateral or unclear changes

Depending on company policy and experience, the amendment may need to be signed by all Parties to the Agreement, or in other cases, only signed by the initiating Party. In general, approval of any amendments should align with the signatures of the original Agreement. If a time is not specified, the amendments will be assumed in force upon signature. For amendments that require changes to production or business practice (for example, incorporating updated GMP requirements), it is advisable to set a reasonable timeline for implementation within the text of the amendment.

IV. Assignment

The assignment term addresses transfer of the roles and responsibilities of a party to the agreement to a third party. Standard assignment terms require that both parties agree on the assignment and that the non-assigning party provide written consent. As assignments generally require an amendment to the agreement (to formally change the named parties), it is common to allow an exemption for assignment to a subsidiary or successor. This prevents a situation where an acquired company or a supplier shifting production sites must amend all their standing quality agreements.

V. Other Agreements/Precedence

Where there are multiple agreements established between the parties, a provision should be included in the quality agreement that clearly specifies under what conditions which

agreement shall prevail. In case of any discrepancy, the inclusion of such a term may prevent unnecessary confusion and conflict.

Quality agreements should outline the quality terms, whereas supply/service agreements should outline the commercial terms. In the unfortunate case of overlap or conflict, the quality agreement, as agreed between the companies' quality units, should prevail over the business agreement for quality matters. For agreements in which the distinction between commercial and quality matters is not entirely clear, companies may wish to include agreed-upon definitions of the terms.

Some companies may have an internal policy requiring the supply/service agreement to prevail under all circumstances. Before accepting such a term in a quality agreement, quality personnel should ask:

- Should decisions on quality matters be made by business personnel?
- How would this policy be justified if challenged by Regulatory Authorities (as applicable)?

VI. Confidentiality

Quality Agreements should have a confidentiality section to define the confidential information that may be disclosed between the Parties during the negotiation or term of the Agreement. A confidentiality provision may not be needed in instances where the parties to the quality agreement already have a comprehensive confidentiality obligation in place (e.g. Supply Agreement, Confidentiality Disclosure Agreement or Non-Disclosure Agreement). As a result, the need for a confidentiality provision in the quality agreement may be contingent on the non-existence of a separate viable confidentiality obligation. Where a previous confidentiality agreement exists, parties should ensure that the term will be sufficient for the Quality Agreement and that the definition of confidential information covers information shared under the Quality Agreement.

VII. Severability

Severability refers to actions in the event that a provision in the quality agreement is determined to be impermissible under applicable law. Typically, the parties agree to use good faith efforts to re-write the problematic provision or delete it in its entirety from the agreement, as opposed to terminating the quality agreement in its entirety because a single provision is unenforceable.

VIII. Governing Law & Jurisdiction

This section of the quality agreement defines two distinct and important legal elements. The governing law provision is an agreement by both parties that the laws of a particular jurisdiction will apply to the contract. The jurisdiction clause dictates the agreed upon venue

for any disputes relating to the Agreement. It is important to note that these are not necessarily the same, for example, Ontario courts can apply Massachusetts law to resolve a dispute if that is the law the parties choose. However, it is generally preferable to use governing law and venue from the same territory, state, or country. Although most templates will include default provisions, the jurisdiction is frequently changed in negotiations to accommodate both parties. It should also be noted that some jurisdictions limit choice of law based on relevance or contacts.

In some cases, parties may opt not to include a specific jurisdiction and venue, but instead use an arbitration clause. Arbitration clauses generally specify the administrator and jurisdiction for arbitration, as well as the location and language. Arbitration clauses should also specify a set of rules to govern any arbitration (for example, the International Arbitration Rules of the International Centre for Dispute Resolution).

IX. Counterparts

This section states that the agreement may be signed at different times and locations, and that all appropriate signature pages may be brought together (either electronically or on paper) to produce one unified Agreement. This is vital in today's business environment, where it is that one paper contract is not physically delivered from location to location. Counterparts allow for.pdf documents to be sent between parties for a more efficient signature process. Companies using counterparts should ensure that they have clear compilation and storage protocols to ensure that a fully unified final Agreement is created and accessible as needed. In cases where a counterpart clause is not included in the quality agreement, original signatures from each party should be obtained on the same original agreement.

TECHNICAL CONTENT

STANDARD QUALITY TERMS

The quality terms set-out the contracting parties' roles and responsibilities as agreed between them and as relevant to the supply or services. Key topics to be considered that will be further discussed in this guidance are:

I. Regulatory Authority GMP Inspections
II. Right to Audit
III. Data Integrity
IV. Documentation/Records
V. Change Notification/Change Control
VI. Annual Product Reviews (APR) / Product Quality Reviews (PQR)
VII. Deviations/Investigations/Out Of Specifications ("**OOS**")
VIII. Complaints
IX. Recalls / Regulatory Reporting
X. Sub-Contracting
XI. Starting Materials/Supplier Management/Supplier Qualification
XII. Validation/Qualification
XIII. Manufacturing (Processing/Packaging)
XIV. Final Product / Final Product Release
XV. Quality Control
XVI. Stability/Sample Retention
XVII. Storage and Distribution
XVIII. Returns

Other notable topics that may be considered, but which will not be discussed in this guidance, include:

XIX. Self-Inspection
XX. Training and Competence
XXI. Facilities (Housekeeping/Pest Control)
XXII. Counterfeits
XXIII. Controlled Substances (DEA Requirements for Registration, Security/Facility Design, Order Forms, Importation/Exportation etc)

Appendix C: Content Matrix provides a summary of recommended topics for various types of supply/service relationships.

I. Regulatory Authority GMP Inspections

Quality regulatory GMP inspections yielding unfavorable results (e.g., warning letters, sanctions, etc.) may have an undesirable impact on the supply chain. This may not only negatively affect each party's business, but also, and more importantly, the public's welfare. Therefore, when dealing with Supplier/Service providers that are subject to regulatory inspections, the quality agreement should clearly outline the expected communication and obligations between the parties pertaining to these inspections.

Depending on the nature of the supply/service relationship, notice of a planned impending regulatory inspection should precede the actual inspection date. For instance, in case of contract manufacturing where the product is the Customer's, advance notice permits the customer to support and be present during the inspection, if desired. In case of unannounced regulatory inspections, the quality agreement may provide a timeline to notify the Customer from the initiation of the audit. However, where the supply/service provider may supply or provide service to many customers, notice of the inspection may not be practical.

In any case, there should be a clear requirement for either party to report any i) regulatory authority action (e.g. sanctions, withdrawal of necessary permits and licenses, etc.) and ii) observations as they relate to the product or services. The timeline for reporting these should be clearly outlined.

In addition, the quality agreement should outline the Customer's access to the inspection report and the form in which it will be shared (e.g. complete report, redacted report, excerpts, etc.). The inspection report may be used by the end customers to perform supplier risk evaluations or even required due to regulatory obligations. Typically, the inspection or audit reports are redacted to include only relevant information related to the product or service supplied. Alternatively, a summary of the audit and audit findings may be provided.

Provisions should also be included to stipulate if the parties should collaborate and agree upfront regarding the reply to observations related to the supply/services in scope of the agreement.

II. Right to Audit

A quality audit of the Supplier/Service provider is an essential component of any qualification program. The audit permits an evaluation of the Supplier/Services providers' ability to meet the applicable laws, regulations, standards, and relevant guidance, as applicable. The recipient of the supply/services should have the right to review and evaluate the Supplier/Service providers' quality systems, procedures, facilities, and documentation, as they relate to the supply/services received or rendered. However, this right to audit should not interfere or impede the Supplier/Service provider's ability to operate their business. Therefore, it is in the parties' best interest to set forth the conditions of the audit. Such conditions may include:

- Advance written notice requirements for routine (e.g. vendor qualification), for-cause (e.g. quality failure) and targeted (e.g. qualify new service for approved vendor) audits
- Routine audit frequency (e.g. annual, biennial, triennial, etc.)
- Provision permitting for-cause audits
- Number of auditors
- Audit duration
- Guidance around what the auditor(s) may inspect / observe
- Use of third party auditors (e.g. Rx-360). The joint audit program allows members to cosponsor audits in a confidential manner.
- Purchase and use third party audit report (e.g. Licensing Rx-360 audit report)
- Share audit report within company group(s)
- Timeline for issuing the audit report
- Timeline for issuing a response to the audit report; as well as the general content of each response to each observation (e.g. root cause, CAPA (corrective action / preventive action), CAPA due date, etc.)
- Requirements for Confidentiality (Any restrictions to access to documents or processes that are considered business secrets/proprietary)

The final terms agreed between the parties should be commensurate with the business.

III. Data Integrity

Data Integrity should be incorporated into the Quality Management System of the Supplier. An initial gap assessment should be performed by the Supplier to detect gaps in the areas of highest risk including Computer System Validation, Manufacturing, and the Quality Control Laboratory. Relevant Corrective Actions should be developed to address any gaps including any interim actions for remediation activities that require longer implementation guidelines or capital investments. ALCOA+ Principles should be followed. (A - attributable to the person generating the data, L – legible and permanent, C – contemporaneous, O – original record (or true copy), A – accurate, Complete, Consistent, Enduring, Available per applicable regulations).

Data Integrity guidelines and regulations that may be referenced for compliance include:

ISPE GAMP® Guide: Records and Data Integrity)
MHRA: GMP Data Integrity Definitions and Guidance for Industry, March 2015
MHRA: GXP Data Integrity Definitions and Guidance for Industry, Draft July 2016
WHO: TRS 996 Annex 5 - Guidance on good data and record management practices, 2016
FDA: Draft Guidance - Data Integrity and Compliance with CGMP, 2016
EMA: GMP Data Integrity Q&A, August 2016
PIC/S: Guidance on Data Integrity, August 2016
Rx-360 Data Integrity Library

IV. Documentation/Records

Maintenance and retention requirements of paper and electronic records, as applicable, should be outlined in the agreement. The retention period for records should be in line with the relevant regulations or guidance documents, if applicable. In case of no governing regulation or guidance, explicit retention timelines for records may be defined. Depending on the nature of the document, the retention times may vary. The agreement may also outline that the documents shall be i) readily retrievable and ii) stored in a manner suitable to prevent damage and loss.

Negotiation over the retention timeframes may be problematic. For example, a Pharma company may request an Excipient supplier to store records for a lengthy timeframe (e.g. seven (7) years). The timeframe may be requested to ensure the Excipient supplier's records are available for the entire shelf-life of the drug product that used the Excipient for investigational purposes, if and when required. As there are costs associated with excessive or lengthy retention requirements, the parties should negotiate these terms.

V. Change Notification/Change Control

Change Notification/Change Control is a top priority section of any quality agreement; it outlines the requirements for the communication, evaluation and the implementation of changes to the supply/service as agreed between the parties.

Change notification permits the Customer to i) evaluate the impact that the change may have on the quality of the supply/service, on internal documentation and systems, and on the regulatory file/dossier, as applicable, and ii) take any required actions (e.g. prepare for revalidation of the drug product, update internal documents or regulatory file/dossier, etc.).

Often one of the more contentious areas for negotiations is those terms pertaining to the approval rights over supply/service provider driven changes. The Customer may seek approval authority over significant changes that impact the quality of the product supplied or regulatory file/dossier. Approval rights are typically acceptable in cases of strict contract manufacturing (i.e. the Customer is the Intellectual Property Owner of the product) and customer-exclusive product supply relationships.

In the case of impact to a regulatory file/dossier, the quality agreement may include a commitment by the supplier not to implement such changes until there is confirmation from the Customer that the change has been received, evaluated and appropriate approvals obtained (e.g. regulatory approval received).

To ensure clear expectations for change control, the quality agreement may spell out:

- Types of changes that require notification (e.g., a detailed list of the types of changes) or a classification of the type of changes (e.g., minor, major, critical, significant, etc.)
- Timeframe for prior notification of changes
- Content to be included with the change notification (e.g. justification, projected timeline for implementation, etc.)
- Approval rights and timeline for approvals
- Method of communicating changes
- Contact details for receiving change notification if different from quality contact.

For increased clarity, a correlating guideline that aligns with the change control procedure of the supplier may be referenced (e.g. "*IPEC Significant Change Guideline for Pharmaceutical Excipients*", USP <1195>: "*Significant Change Guide for Bulk Pharmaceutical Excipients*", etc.).

VI. Annual Product Review ("APR")/ Product Quality Review ("PQR")

Preparation of APR/PQR, covering each commercial batch produced within a specified review period, is a regulatory requirement for both finished drug and API products. This section may outline i) the party responsible to prepare, review and approve the APR/PQR, ii) the expected content of the APR/PQR, including a summary of any changes, deviations, recall events, trend analysis and CAPA, iii) reference to governing regulation or guideline, iv) clear delineation of the review period, v) the conditions under which the Customer may review and approve, if applicable, the APR/PQR and vi) how the document is to be shared between the parties.

VII. Deviations/Investigations/Out of Specification (OOS)

Should the Customer receive notification of deviations or OOS? Under what conditions or timelines are notifications required? Should the Customer have approval authority over the deviations/OOS?

Answers to these questions are dependent on the supply/service relationship. For specific types of supply, such as excipients or API, or services, such as transportation or warehousing, the quality agreement may simply require the Supplier to have a system in place to conduct investigations. However, for finished product supply or customer-exclusive products, there may be heightened governance with respect to Customer notification and Customer's review and approval of the deviation prior to the commercial release of the product.

In any case, the following content may be considered:

- The types of deviations that require notification (e.g. minor, major, critical and include respective definition), if any
- The requirement for the Supplier to notify the Customer of serious product issues identified after the Supplier's release of the product
- If notification is warranted, the timeline for the notification

- Requirements of the investigation content (e.g. investigation, root cause analysis, historical review, CAPA, product disposition, etc.)
- Timeframe for completion of the deviations/OOS and provisions for extension
- Customer approval rights, if any
- If Customer approval is warranted, indicate whether the Customer approval of the deviations/OOS shall precede the Supplier's release or shipment of the product

VIII. Complaints

Despite best efforts and sound quality systems, quality defects or issues with product supply/services unfortunately do arise and are discovered.

The complaint process requires evaluating, investigation, addressing the defect or issue, and taking measures to prevent future re-occurrence. The implementation of a comprehensive and efficient complaint handling process between the parties may act to ensure the safety of the end user and makes good business sense.

A comprehensive complaint section delineates the mutually agreed:

- Process and timeframe for complaint submission
- Method of providing supporting samples/documentation
- Requirements of the investigation (e.g. investigation, root cause analysis, historical review, CAPA, product disposition, etc.)
- Timeframe for completion of the complaint investigation and provisions for extension
- Party(s) responsible for final review and approval
- Party responsible to reply to the complainant, as applicable

IX. Recalls/ Regulatory Reporting:

Companies supplying products to other companies or directly to the public are legally and ethically responsible to ensure the rapid recall of suspected or confirmed defective products. This is especially critical in the case of supply / services impacting marketed pharmaceutical products affecting the public's safety. A comprehensive and well written quality agreement that incorporates content to aid a rapid recall may mitigate any undue risk to the public.

To facilitate a clear understanding between the parties, some consider the following:

- The timeline for communicating the discovery of a potential for a recall
- The timeline for completion of the recall investigation (if the parties expect expedited investigations)
- The party responsible to conduct the recall investigation
- The expected content for the recall investigation, including full supply chain traceability
- The party responsible for the final decision of the recall of the product

- The party responsible for regulatory authority reporting, when warranted
- The party responsible to execute the investigation
- The party responsible to execute the recall
- The requirement for supplier to conduct periodic challenges of their recall system to ensure expedited retrieval of traceability information
- The requirement for supplier to implement systems such that the recall can be put into operation during and outside normal business hours (e.g. include out of office contacts)

X. Sub-Contracting

Any outside companies that are being used to provide product/services should have attention brought to their activities and responsibilities in the Subcontractor Section. The services may include, but not limited to, sterilization services, manufacturing, packaging, labeling, testing, warehousing, and/or transportation. This section shall define which party will be responsible for the actions of the subcontractor and how the subcontractor's activities will be in alignment with the agreement. The parties of the agreement should state their requirements for a subcontractor qualification process and the expectations for sharing such supporting qualification documentation.

Subcontractor names and specific activities performed may be included in an attachment or appendix of the agreement.

If not already outlined in the Audit Rights and Change Notification sections, it would be advisable to include the right to audit the subcontractor and the importance of Change Notification being provided through the supply chain.

XI. Raw Materials/Supplier Management/Supplier Qualification

The qualification of in-coming starting materials used to manufacture/package the product supplied should be defined. Specifically, the party responsible should be identified and the qualification requirements outlined. In cases where the Supplier is responsible for the qualification, the Customer may request to exercise some quality oversight over the supply chain. In this case, the boundaries of this quality oversight should be agreed. For instance, can the Customer review the audit report/quality agreement between the Customer and starting material supplier? If so, under what conditions may the audit report/quality agreement be reviewed (e.g. during on-site audit of the Supplier, redacted, under the conditions of a confidentiality agreement, etc.)?

Where applicable, the quality agreement should stipulate the requirement to purchase from approved starting material suppliers in accordance with the marketing authorization/drug application.

The quality agreement should also allocate responsibilities between the parties for the establishment of the specifications and testing methods and the requirements for incoming sampling and storage (e.g. storage conditions and controls) of the starting materials.

Depending on the type of material supplied, the quality agreement should include the obligation for the supplier to provide statements/certifications related to the starting materials. For example, the supplier may be required to provide:

- GMP certificate / regulatory compliance
- Transmissible Spongiform Encephalopathy ("**TSE**")/Bovine Spongiform Encephalopathy ("**BSE**")
- Residual Solvents
- Elemental Impurities & Metal Residues
- Animal Origin Status
- GMO Statement
- Cytotoxicity

XII. Validation/Qualification

The quality agreement should clearly define each party's responsibilities as they relate to the Validation or qualification (IQ, OQ, PQ) for the facilities, utilities, equipment, test methods, cleaning, process, and computerized systems, as applicable to the supply/services. Depending on the nature of the relationship, the following should be agreed upon:

- The validation regulation or guidances that apply.
- The validation approach that may be applied (e.g. risk based, bracketed/matrix, etc.)
- The party responsible for maintaining a Validation Master Plan and the conditions under which this document may be shared
- The party responsible for generating and executing the validation/qualification protocol and reports and the conditions under which the validation/qualification protocol and reports may be made available for review
- Consideration for requalification/revalidation

XIII. Manufacturing (Processing/Packaging)

The manufacturing and packaging section of a quality agreement details the manner in which the products are fabricated. This section may provide mutual agreement that the products will be manufactured in accordance with specifications, guidelines/regulations and regulatory file/dossier, as applicable. In the event there is an issue with the manufacturing or packaging of the product, the section may also address the agreed action and/or approval for reprocessing and rework of the products. The product label content may also be specifically outlined, as well as any labeling control and destruction requirements.

Other topics typically outlined relate to the manufacturing programs or controls employed to deter contamination (e.g. cross contamination, micro contamination, metal, etc.), and the

applicable governing guidances, if any (e.g. ISPE's Risked-Based Manufacturer of Pharmaceutical Products, ICH Q9, etc.). The agreement may include a provision prohibiting the introduction of non-desirable compounds (e.g. hormones, penicillin, cytotoxic compounds, cephalosporins, beta lactams, pesticides, herbicides, rodenticides, etc.) to the production facilities/equipment common to the product supplied, unless otherwise mutually agreed.

For Sterilization services or sterile products, adherence to a recognized standard (e.g. ISO 11137, 11135, etc.) can be called out as well as for bio burden testing (e.g., ISO 11737), as applicable. The process should ensure that materials be sterilized in a consistent and controlled manner appropriate to their intended use in accordance with applicable regulations and in compliance with the product's specifications. The quality agreement may specify the required content of sterility certificates.

XIV. Final Product / Final Product Release

This section should detail the roles and responsibilities for final release of the product and the party responsible for finished product release testing. Consideration may be given to Regulatory Authority requirements, where applicable, for release in different Territories and shipment under quarantine provisions. The section should define the responsibilities for manufacturer's release and the release requirements for commercial distribution (e.g. finished drug product and medical device supply), as applicable.

The documentation requirements for the release of the product, such as a Certificate of Analysis or Certificate of Conformance, GMP statement may be outlined and vary depending upon jurisdiction and regulatory requirements, as applicable. Some companies require review of batch records prior to the final release.

XV. Quality Control

To assure the quality of starting materials (e.g. API, Excipients, advanced starting material, etc.) or finished product, the quality agreement should describe the testing requirements and other quality controls agreed between the parties.

Each product should be tested according to the agreed upon specification and according to the regulatory file/dossier, where applicable and verified and released by the responsible QC personnel.

This section may include other provisions such as i) the laboratory equipment shall be qualified, calibrated, and maintained, ii) compendial changes shall be incorporated on or before the effective date and iii) data integrity policies and procedures shall be implemented to ensure the accuracy, completeness and consistency of raw data as per applicable regulations.

The quality agreement may also delineate the party responsible to:

- Establish the specification
- Approve the specification
- Validate the method (non-compendial methods)
- Approve the method validation (non-compendial methods)

XVI. Stability/Sample Retention

Stability data studies are required to establish the retest and/or expiry date for the product. An on-going stability program confirms that the product will meet the specifications while stored in the designated packaging configuration for the specified period.

The quality agreement should outline the governing procedure and/or guidelines in which the stability studies will be conducted.

Furthermore, the following may be agreed:

- The Party completing the testing
- The Party with Review and approval authority
- Obligations of communicating the testing results

The conditions in which the end customer may access the stability protocol, report and raw data that support the product shelf-life may also be negotiated (e.g. complete report during on-site audit, stability statements/profiles, etc.).

Unless otherwise outlined in the deviation investigations section, the requirements for stability OOS should be outlined. Specifically, notification timelines for stability OOS should be agreed between the Parties as there may be market action implications that directly impact the welfare of the public.

Sample Retains – the storage requirements for sample retention (quantity and time period) of the QA retains should be described per suppliers internal procedures.

XVII. Storage and Distribution

To ensure the integrity of the product throughout the supply chain, this section of the quality agreement may describe:

- Storage/transport of the product under the recommended/required environmental conditions
- Warehouse/carrier temperature and humidity monitoring and controls
- Control and segregation of quarantined and rejected products
- The use of plastic or heat-treated pallets (in accordance with International Plant Protection Convention (IPPC) standards (e.g. ISPM 15)).

XVIII. Returns

The agreement may delineate how and under what conditions a product may be returned to the Supplier. There may be a requirement that the Supplier maintain a procedure to ensure returned products are identified and segregated and records are maintained to avoid any unintentional use.

Where applicable, the circumstances under which the returned product may be returned to stock or destroyed may be outlined. This may include the requirements for a documented evaluation which may include retesting, affirmation that the return stock was maintained under the required storage conditions, and the party responsibly for the disposition.

Other information that may be considered for inclusion in the quality agreement includes:

- Contact List
- Product List
- Authorized Facilities/subcontractors (e.g. the site performing the activity)

Best Practices for Quality Content Terms:

- If using templates, edit the content so it is comprehensive, relevant and focused to the scope of the supply/services and the standards under which they are produced and supplied.
- Ensure timelines, when warranted, are explicitly defined:
  - Such as three (3) days; including business or calendar specification.
  - Words or phrases such as “promptly” or “as soon as reasonably possible” lend no understanding between the parties.
- Ensure language is easy to read and comprehend. Quality agreements must be read and understood by quality personnel, not only lawyers.

Negotiation and Review

[Note: This chapter does not cover the "periodic review" of quality agreements every 2 or 3 years. "Review" in this chapter is restricted to the negotiation phase.]

Prior to starting negotiations, the expectations of both parties should be clarified, e.g. scope of the agreement (products, services, sites to be covered), use of a standard template vs. use of an individual document. Furthermore, it is recommended to mutually agree upon a timeline for review at the very beginning.

Basically, negotiation will become significantly easier and faster if standardized templates – ideally pre-reviewed by Legal – are used. The "time argument" will also be most convincing for a number of suppliers or customers to accept the use of a standard template ("*if we can agree upon the ABC template we may be ready for signature within two weeks*").
In case one party insists on the use of its individual agreement, however, there are still different possibilities how both parties may benefit from the use of a standardized template during the negotiation phase:

- The template may be **used as a basis** for a (slightly) modified, customized draft agreement
- **Certain sections** of the template may be used when drafting an own agreement ("tool box")
- The templates‟ wording may be **used to resolve dispute** if mutually understood as good industry practice.

Hence a standardized template constitutes 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. Individuals negotiating should have full knowledge of the rationale behind the text. It is best practice to provide justification for any changes to major terms, to explain why a certain paragraph is written as it is, or to have a reasoned justification ready for any non-negotiable elements to explain why the clause cannot be changed. Where necessary or requested by either party, country-specific or product-specific requirements may be added to the standard text.

Any alterations should clearly be indicated by the amending party to the other party as this will help to achieve one of the major aims of the template use – speedier agreements. 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", i.e. redline

rather than clean versions should be used. A "cleaned" version would be created only directly before signature, after all parties are satisfied with the draft agreement.
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.

Best Practices for Negotiating a Quality Agreement:

- Use of standard templates (e.g. provided by industry associations) will save time if the products fall into a standard category.
- Proposed changes to the (standard) template should be explained.
- Quality should negotiate with Quality (involving others as needed).

Scope

Structure

Framing Content

Technical Content

Negotiate

Review

Signature

Maintain

The Quality representatives of Customer and Supplier 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.

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 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 recommended, 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 representative's 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:

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 endeavors" (but not "best" endeavors).

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.

Best Practices for Reviewing a Quality Agreement:

- Language should be simple (i.e. "non-legal") and unambiguous.
- Review by Legal is recommended if changes are made to template. Clearly identify changes to expedite review.
- Be careful with terms like "guarantee" or similar.
- Ensure primary text and any annexes or appendixes align.

Signing and Maintaining Agreements

The purpose of a signature is to authenticate writing, or provide notice of its source, and to bind the individual entity signing the writing by the provisions contained in the document. Signing the document is not simply writing one's name on a piece of paper. The signature means that the person agrees to the conditions outlined and also agrees to perform the actions stated in the contract. The person signing pledges to follow the rules and also pledges to accept the consequences if they fail to do so.

Scope

Structure

Framing Content

Technical Content

Negotiate

Review

Signature

Maintain

Ordinarily a signature can be affixed in a number of different ways. It can be hand written, digital or electronic, printed, stamped, or photographed. A hand written or "wet" signature is a mark that identifies the individual who created it. It commonly spells out a person's name. Unless otherwise legally expressed, a signature can be written with loops, ascenders, descenders, special characters or signs; as long as it remains consistent from contract to contract otherwise the validity of the signature can be contested.

Alternatively, digital signatures may be used. There can be issues though if both parties that are to sign the agreement do not have access to the same exact electronic system for digitally signing documents. If this is the case wet signatures may have to be used. Parties should also ensure that the jurisdictions in which the Agreement will apply acknowledge the legal validity of digital or electronic signature. Most countries have passed "e-sign" laws to this effect but a few outliers remain.

Most jurisdictions now also accept facsimiles of actual hand-written signatures as legal signatures. Using facsimile signatures means that the documents must be faxed back and forth several times until all parties have signed off. One word of caution is to be sure that the signatures are strong and legible as some times during repeated faxing the original signatures can become very faded and illegible.

Authority to sign

Authorization to sign contracts is normally addressed in a corporation's bylaws and / or in resolutions of the board of directors. It is very important to ensure that any party signing the agreement has the legal authority from the company to do so. Many companies may also wish to include a signature from the quality department to indicate they have reviewed the terms. It is usually a good idea as part of the signature to include the printed name, title and company of the individual who is to sign the agreement. If any of these items do not match what is stated elsewhere in the agreement it would be a good idea to vet the individual before the signature is made. In some cases it may be appropriate to add a clause such as:

Each person signing this Agreement represents and warrants that he or she is duly authorized and has legal capacity to execute and deliver this Agreement.
Unless an alternative effective date is provided, a Quality Agreement is generally effective upon the signature of both parties. However, a company's obligations are not completed once the agreement is finalized.

Maintaining Quality Agreements

Existing non-disclosure agreements between parties and a company's security protocols will place constraints and controls on the release of documents; ensure that storage of and access to the agreements remains in compliance.

A common practice is for signed and completed Quality Agreements to be stored in a central repository so that all agreements are kept together and easily searched or controlled by one group (often Legal or Quality Assurance). Hardcopy documents can be scanned and loaded into an Electronic Document Management System (EDMS), while the original can be safely filed with the owning department. This practice facilitates wider use and visibility by many groups.

Notify key users, that a new agreement is in place- so that any agreed upon contacts or authorities within the organization are added, where applicable to the appropriate quality systems (e.g. Change Communication and CAPA systems). Agreements containing more technical or non-standard commitments, may require specific training.

Notifications can be accomplished manually or automatically. Many EDMS or Learning Management Systems (LMS) can be set to automatically notify a pre-selected user group that a new Quality Agreement has been loaded and approved. This can directly trigger a review of the agreement and any required actions. In lieu of automated systems, a simple email-group list can accomplish the same thing, directing employees to the electronic location of the document.

One best practice to facilitate training and eliminate inconsistencies with interpretation of Quality Agreements (often written in legalese or difficult to understand language) is to create a Summary Document for each agreement that extracts and plainly lists the deliverables, notification commitments, and timeframes that have been agreed to in a particular Quality Agreement. This is particularly useful for quick reference situations, and to avoid having employees read through an entire legal document, or avoiding different interpretations of what is required. Here is an outline of the steps to create.

a. Summarize key deliverables for each agreement into a 1-page document
b. Make the document easily accessible and linked to or reference the official agreement

c. Communicate agreement details using the 1-page summary rather than the full agreement.
d. Easily reference the Summary Document when needing to see commitment details

You can create a standard template to capture all deliverables, notification timeframes, or actionable items and summarize them on 1-page. This can make compliance, reference, and look-up of details much easier for individuals and groups responsible for complying with the agreement, and removes much of the interpretation issues that often accompany having people read through complex legal agreements. You can add paragraph or section numbers to facilitate going back and reading the original agreement in context. The summary sheet can be created and approved in the EDMS alongside the official agreement. For obvious reasons, it is important that this summary document be reviewed and approved internally to be sure that everything is captured and that none of the commitments have been missed. See an example Quality Agreement Summary document in Figure 3.

Quality Agreement Summary

CUSTOMER:	Products:	Effective Date:
QAG Doc #:		

The following items are actionable responsibilities extracted from the effective Quality Agreement above:

SECTION	ACTIONABLE ITEMS FOR CLIENT
8.4	CLIENT will generate manufacturing records for product and submit them to CUSTOMER for approval prior to use and prior to any changes.
8.6	CLIENT will generate SOPs for product specific analytical methods and submit them to CUSTOMER for approval prior to use and prior to any changes.
8.6	If contracted, CLIENT will generate Method Validation Protocols for product and submit them to CUSTOMER for approval prior to use and prior to any changes.
9.2	Testing will be completed not more than 30 days from the date of manufacture
9.3	Maintain enough retention samples for 3X testing for 1 year past shelf life
9.4	If contracted, CLIENT will generate Stability Protocols for product and submit them to CUSTOMER for approval prior to use and prior to any changes.
10.1	Notification within 3 business days of significant nonconformances or confirmed OOS during product manufacturing or testing
10.2	Notification within 3 business days of significant nonconformances discovered after product delivery.
10.2	If CUSTOMER discovers nonconformity after delivery, CLIENT will complete the investigation within 15 days, otherwise provide an interim report at 15 days. If CLIENT agrees with nonconformity, CAPA plan will be sent to CUSTOMER within 10 days.
10.3	CoA, CoO, and CoC provided upon batch release by QA
10.3	Copies of completed batch record and analytical test data provided by CLIENT Project Management
10.5	CLIENT will provide requested information for any product complaints or regulatory requests within two business days.
10.6	CLIENT will retain batch record documentation for no less than 10 years or for the duration of the Master Agreement.
11.1	Notification within 1 business day of an inspection by any Regulatory Agency that directly relates to the CUSTOMERs product.
11.1	Notification within 1 business day of receipt of an inspection report by a Regulatory Agency that directly relates to the CUSTOMERs product.
11.1	Copies of Regulatory inspection reports and CLIENT responses will be sent within 1 business days of responses being sent to the Regulatory Agency for inspections that directly relates to the CUSTOMERs product.
14.1	If required, CLIENT will generate Process Validation Protocols for product and submit them to CUSTOMER for approval prior to use and prior to any changes.

Fig. 4. Sample Quality Agreement Summary Document

Best Practices for Maintenance of Quality Agreements

- Store Quality Agreements electronically in a central repository to make them more readily accessible.
- Notify impacted employees about new agreements using automated systems built into EDMS/LMS systems or simply by a group lists within your company email system.
- Create a Summary Document for each Quality Agreement that plainly states deliverables, notification commitments, and contacts etc.
- Comply with confidentiality and security requirements.

One of the more important tasks after signing a Quality Agreement is ensuring setup of systems in order to make sure there is compliance to the agreement. Ideally, during the negotiation process, any provision that cannot normally be complied with would be identified and removed or discussed with the other parties, but if not, a system for monitoring/periodic review and ensuring compliance needs to be implemented. Example of common tasks include adding a list of products to a change notification system, establishing document deliverables for products, adding defined customer contact info to official systems.

These are just a few of the key tasks that need to be done after an agreement is signed. Because proper compliance to the agreement will often rely on these post-signature tasks, another best practice is to include these tasks as part of your internal Quality Agreement procedure or perhaps as a checklist of tasks to be completed.

Finally, your internal procedure should establish a process and timeframes for how long Quality Agreements are in effect and what to do when they expire. This should be agreed to during the negation process with the other party, but internal procedure should document how to track and manage Quality Agreement Timelines, including the considerations below:

a. Does an agreement ever expire?
b. Will a document expire after a certain number of years?
c. Can it be auto-renewed without re-signing?
d. Can Product Lists or Appendices be updated without re-review or re-signing the entire agreement?

These are some of the questions that need to be addressed in your procedure and brought up during the negotiation process in order to avoid issues after the agreement has been in effect for several years.

Best Practices for Maintenance of Quality Agreements

- Include any post-signature tasks in your internal procedure and setup a checklist to be sure these items are completed for each new Agreement.
- Allow for Product Lists and other Appendices to be updated without requiring the entire document to go back through review and revision.
- Include Expiry or Renewal guidelines in your internal procedure. Tie expiration to Supply Agreement (with noted surviving terms).

Conclusion/Summary

Conclusion

This Rx-360 Best Practices Quality Agreement Guide is intended to assist both Manufacturers and Suppliers in efficiently managing the initiation, negotiation, implementation, and ongoing maintenance of quality agreements. It is intended to be a reference guide for best practices and should be used to help streamline processes and provide simplified solutions for common tasks associated with Quality Agreements

The Supplier-Led Working Group (SLWG) considers this a living document and will update it as needed based on the most current industry and regulatory practices. We welcome any questions or comments you may have on the material in this document.

As with other SLWG documents, it attempts to highlight the perspectives and needs of both Manufacturers and Suppliers, while trying to identify the best practices that enable the industry to best meet the needs of our patients.

The information included is for reference only and should not be substituted for following regulatory requirements for your particular product or application.

The best practices included were shared and collected from multiple industry volunteers representing both manufacturers and suppliers, most of which are quality agreement specialists in their fields. This document would not have been possible without their hard work, insight, expertise, and dedication to the project.

Thank you!

Version 2.0 Review Team

Name	Company
Ken Crossley	*VWR*
Monica Pena	*Daiichi Sankyo*
Elayne Kimmett	*Biogen*
Rainer Fendt	*BASF*
Dee Ledwin	*Daiichi Sankyo*
Tom Jiang	*Daiichi Sankyo - Intern*
Steffen Hartwig	*MilliporeSigma*

Appendix(es)

Appendix A. Content Regulatory References

This list of references is provided as a general guide to regulatory and guidance documents commonly used or referenced in Quality Agreements. Additional regulations and guidance may apply depending on the type of product/service provided and the jurisdictions involved.

Topic	Regulations/Guidance Document
Pharmaceutical Drug Products	US 21 CFR Parts 210, 211, 1300-1317, 1321 EU Directives 2001/83/EC as amended, 2003/94/EC as amended and the current relevant EU Rules and Guidance for Pharmaceutical Manufacturers and Distributors Canadian GMP Guidelines (Div. 2, Part C of the Food and Drug Regulations) WHO Guideline on GMP (current version) **QTA Guideline:** FDA Guidance for Industry Contract Manufacturing Arrangements for Drugs: Quality Agreements
Active Pharmaceutical Ingredients	ICH Q7: Good Manufacturing Practices Guide for Active Pharmaceutical Ingredients EudraLex The Rules Governing Medicinal Products in the European Union, Volume 4 Part II Basic Requirements for Active Substances used as Starting Materials Canada: Good Manufacturing Practices (GMP) Guidelines for Active Pharmaceutical Ingredients (APIs) (GUI-0104)
Excipients	USP General Information Chapter <1078> :Good Manufacturing Practices for Bulk Pharmaceutical Excipients

Medical Devices	Council Directive 93/42/EEC on Medical Devices as amended Council Directive 98/79/EEC on in vitro diagnostic medical devices as amended ISO 13485 (collectively referred to as "EU Directives") FDA QSR - 21 CFR Part 820 Medical Devices Regulations (SOR/98-282)
Transportation	ISPM 15
General Chemicals	ISO 9001
Other Guidance Documents	Other Guidance documents developed by the International Conference on Harmonisation (ICH): ICH Q1A(R2): Stability Testing of New Drug Substances and Products ICH Q1B: Stability Testing: Photostability Testing of New Drug Substances and Products ICH Q1C: Stability Testing for New Dosage Forms ICH Q2(R1): Validation of Analytical Procedures: Text and Methodology ICH Q9: Quality Risk Management

Appendix B. Industry Guides and Templates

- Excipients:
  - IPEC's "The IPEC Quality Agreement Guide and Template" (2017)

- APIs:
  - Active Pharmaceutical Ingredients Committee's "Quality Agreement Guideline & Templates APIC" Version 02 (July 2017)

- Single-use Biopharmaceutical manufacturing products:
  - Bio-Process Systems Alliance's "Consensus Quality Agreement Template" (2014)

Appendix C: Content Matrix

Quality Agreement Topic	Quality Agreement Type														
	Supply						Service								
	API	Excipient	Pharma Product	Medical Device	Packaging Components	General Chemical/ Ancillary Materials	Calibration Services	Medical Communication Call Centers	Carrier	Contract Lab	Investigator Initiated/Collaboration Studies	Sterilization	Warehouse/ Distribution	Waste Facilities	General Services
Regulatory Authority GMP Inspections	X	*	X	X	*		X	X	*	X	X	X	*	X	*
Right to Audit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Documentation /Records	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Change Notification /Change Control	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Annual Product Reviews/Product Quality Reviews	X		X												X
Deviations/Investigations/Out of Specification	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Complaints	X	X	X	X	X	X		X	X	X	X	X	X		X
Recalls / Regulatory Reporting	X	X	X	X	X	X		X					X	X	X
Sub-Contracting	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Raw Materials /Supplier Management/ Supplier Qualification	X	X	X	X	X	X									X
Validation/Qualification	X	X	X	X	X	X			X	X	X	X	X	X	X
Manufacturing (Processing/Packaging)	X	X	X	X	X	X					X				X
Final Product / Final Product Release	X	X	X	X	X	X						X	**	X	X
Quality Control /Data Integrity	X	X	X	X	X	X				X	X	X			X
Stability	X	X	X			X				**	X				X
Storage and Distribution	X	X	X	X	X	X			X		X	X	X		X
Returns	X	X	X	X	X	X					X		X		X
Self-Inspection	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Training and Competence	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Facilities (Housekeeping/Pest Control)	X	X	X	X	X	X			X	X	X	X	X		X
Counterfeits			X												X

* Supplier is typically not subject to regulatory authority inspections; however, section may be included in cases where the Customer may require the Supplier to help address any inspection findings as they relate to the supply/service; or for the pharmaceutical company to communicate such observations to the Supplier.
**If contracted for such an activity.

API	API Manufacturer, non-compendial excipient
Excipient	Manufacturer of compendial excipients
Pharma Product	Drug product intermediates, drug products
Medical Device	Medical device manufacturers
Packaging components	Manufacturer of primary packaging components having product contact (e.g. bottles, caps, polyester, blister material, desiccants) Product contact consumable materials (e.g. filters, tubing disposable pipettes)
General Chemical/Ancillary Materials	General Chemicals/ Non-product consumable materials (e.g. bundle wrap, non-printed corrugated shipping cases, shipper labels)
Calibration Services	Service provider for testing/calibration of equipment or instruments used in API/excipient/Product manufacturing or primary packaging operations or laboratory equipment.
Medical Communication/Call Centers	Question or Complaint call centers
Carrier	Transporter of API, Drug Product, Finished Materials
Contract Lab	Analytical or Microbiological testing laboratories used to support release of product or stability testing
Investigator Initiated studies	Clinical studies initiated and managed by a non-pharmaceutical company researcher (e.g. individual investigator, institution, collaborative study group, cooperative group) who, as the sponsor, is responsible for the conduct and management of the study.
Sterilization	Sterilization Services
Warehouse/ Distribution	Stability storage facilities for drug products and controlled substances Warehouse facility for storage of API, excipients, drug products, primary packaging components having product contact Distribution or Product Return Centers
Waste Facility	Waste facility for destruction of products
General Services	

For more Information you may contact:

Rx-360

info@rx-360.org

301-710-9399