PART I
Coordination and Communication between Partners in Outsourced GMP Activities

What information should be communicated between a contract manufacturer and the firm who gives the contract? Does this differ from changes or events that must be reported to regulatory agencies and if yes, how? When does a change-control need approval of both parties prior to implementation, and when can it simply be reported to the firm giving the contract after the fact, or not at all as the case may be? Beyond change controls, what other events or activities should be reported to the firm giving the contract? And of equal importance, how can this best be accomplished in the least burdensome manner and remain compliant with the relevant regulations and guidance? Seems overwhelming, doesn't it?

The guidelines and guidance from regulatory authorities regarding outsourced GMP activities provides a starting point for trying to make some sense of this. A thoughtfully constructed Quality Agreement simply makes good business sense, in addition to being a regulatory agency expectation for the FDA and EMA. Firms should have SOP(s) describing the types of shared activities that require Quality Agreements and how Quality Agreements are developed, implemented and reviewed. The content may be provided in a company specific template for various types of business arrangements to facilitate consistency in implementation. On size does not fit all, and Quality Agreements scope and breadth should consider the overall potential impact to product quality and patient safety.

INTRODUCTION

Outsourcing GMP activities including manufacture and testing of APIs and drug products is a common practice within the pharmaceutical industry. Regulatory agencies hold the person or firm who owns the license or manufacturing authorization responsible for the quality of the product regardless of the firm that performs the actual "manufacturing" operations. Thus, while activities can be outsourced, accountability for final product quality remains with the license holder. Contract manufacturers must comply with GMPs and those who purchase their products or services are accountable to qualify them and provide ongoing oversight. Sound Quality Agreements serve to formalize responsibilities of the partners in outsourced GMP activities. For ease of understanding, we use the EMA terms "contract giver" and "contract recipient" in this article.

REGULATIONS and GUIDANCE ASSOCIATED with QUALTY AGREEMENTS:

The EMA and FDA both expect that the parties subject to outsourcing will have a Quality Agreement that clearly delineates the responsibility of the parties. The governing requirements from the EMA are highlighted in the EU GMP Guide, *Chapter 7, Outsourced Activities*, which was updated and effective in January 2013 to address all outsourced activities, not just contract manufacture. This chapter addresses control that should be applied to outsourced activities, including the preparation and periodic review of Quality Agreements. Prior to outsourcing any activity the contract giver should ensure and document that the contract recipient is suitable and qualified for the specific activity. This includes initial vendor qualification and frequently an on-site audit, ongoing monitoring and periodic assessment often including on-site audits.

The FDA does not have a regulation that specifies a quality agreement but they published a *draft guidance* in May, 2013 titled *Guidance for Industry, Contract Manufacturing Arrangements for Drugs: Quality Agreements*. The applicable regulations include 21CFR 211 *Subpart E*[1], and 21CFR *820.50* that specifies Purchasing Controls for Devices and Combination Products. The controls specified in Section 7, Materials Management of *ICHQ7* applies both to the FDA and EMA regulated firms regarding manufacture of APIs. An *article* that compares the US and EMA requirements for Quality Agreements provides some useful insight on their structure and requirements.

QUALITY AGREEMENT TEMPLATES

Part of the purpose of a Quality Agreement is to coordinate communications and responsibilities between the parties sharing GMP activities under contract. For a contract manufacturer it is generally prudent to have a "standard" Quality Agreement template that serves as the starting point for negotiations with clients that lead to the final agreement. Changes to this standard template may be made based on specific product requirements or the requirements of the regulatory authorities in countries where the drug product is sold. The EMA also expects written agreements between different geographic sites within the same corporation that share in different steps of manufacture and testing. These are often referred to as service level agreements. We do not address those in this article, but it is prudent to be aware that the expectation exists. Firms should also have quality agreements with suppliers of excipients and other critical raw materials who have also been qualified and are subject to ongoing oversight.

The complexity of the quality agreement should be commensurate with the potential risk to product quality and patient safety. Thus, an agreement between the API manufacturer and dosage form manufacturer may include more detail than an agreement between an API manufacturer and a supplier of a non-critical raw material used in early synthetic steps of a starting material. Selected Quality Agreement templates have been prepared by a variety of trade organizations, three of which are provided here below. Firms might consider which ones best meet their specific needs and use them, or some combination, as the starting point for developing their own template.

- *IPEC-Europe* Template for Quality Agreement specifies best practices for a Quality Agreement between a dosage form manufacturer and supplier of an excipient.
- The *Bulk Pharmaceutical Task Force* provides a template for Quality Agreements for use by firms that make and purchase APIs.
- *APIC Quality Agreement Templates and Guide*. This also includes a section of additional references.

Events and changes that are reported to partners in the Quality Agreement are generally more broad than changes and events that are to be reported to regulatory authorities.

CHANGE CONTROL and REPORTING OF CHANGES WITHIN a QUALITY AGREEMENT

None of the Quality Agreement templates address in detail those changes which need prior approval of the contract giver, those where they need to be informed or those changes where they do not need to be informed. Many simply specify that "major"

[1] Subpart E, *Control of Components and Drug Product Containers and Closures*

changes must be reported, though this provides little actionable assistance. The examples provided below are not meant to be all inclusive and should be evaluated for applicability considering the nature of the product being produced and the history and expertise of the parties. Regardless of the category of the change(s), they should be documented, justified, and results evaluated to ensure correct implementation. The extent of the studies or (re)validation necessary should be based on the risk to product quality, safety and efficacy. For purposes of this discussion, changes can generally be divided into three categories:

- **Changes which the contract giver must approve prior to implementation, for example:**
  - Changes that require notification of a regulatory agency (see the selected references in Part II, particularly the last reference which published May 29, 2015). The contract giver should provide the relevant information in the regulatory filing so that the contract acceptor may have this information on-site to assist in decision making discussions.
  - Change in API or drug product specifications
  - Changes that have potential for significant impact on product quality, for example use of recovered solvents rather than virgin solvent. The person issuing the contract should identify the critical parameters and features of manufactures and testing that are necessary to ensure product quality. These parameters will vary from product to product.
  - Changes in equipment type
  - Major renovation of a facility that may impact environmental monitoring results, flow of product(s) or potential cross contamination
  - Changes in the batch record for reasons other than editorial clarity
- **Changes about which the contract giver must be informed, for example:**
  - Addition of a new product of the same type already made in the facility
  - Changes in SOPs that may be indirectly relevant to manufacture of the product
- **Changes that do not require involvement or notification, for example:**
  - Ongoing routine maintenance and equipment calibration where nothing unusual or out of calibration is noted
  - Routine changes in SOPs for clarification or to provide more detailed instruction; SOPs that address product specific requirements or "established conditions"[2] may have different burdens.

Based on the nature of the change itself, it may be necessary to re-validate at least some unit operations in the manufacturing process. Major changes may require that one or more lots of product are placed on accelerated stability evaluation and/or long term stability evaluation to ensure that the change does not have an unintended change on the long term stability or expiry of drug product. The retest date of API may need to be reconfirmed after major changes are made. Less frequently, and also depending on the nature of the product, major changes may require repeating BA/BE evaluations.

OTHER EVENTS that MAY REQUIRE COMMUNICATION BETWEEN QUALITY AGREEMENT SIGNATORIES

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[2] ***Guidance for Industry, Established Conditions, Reportable CMC Changes for Approved Drug and Biologic Products*** This is the last item in the listing of references in Part II

In addition to communication of change between the two parties it is important that the quality agreement specify other events that must be reported by the contract recipient. Reporting of some events is generally specified to occur within a time range, some as short as 24-48 hours. During an audit of the contract recipient site, the contract giver should evaluate changes that occurred during the time period covered by the audit to ensure that changes have been communicated consistent with the Quality Agreement. Examples of changes that may need to be communicated between the two parties include but are not limited to:

- Initiation or notification of inspections by Regulatory Authorities and their outcome; this includes enforcement actions such as untitled letter or warning letter, import alerts, license suspension or limitations placed on products covered by a GMP certificate
- Information that may impact the quality of a product already sold or in the marketplace; for the US, this may also require submission of a Field Alert Report by the NDA/ANDA holder depending on the nature of the information.
- Out of Specification and Out-of-trend results prior to any resampling or retesting; OOS events must be investigated even if the contract giver does not request or pay for the investigation
- Receipt of customer complaints and adverse events by the contract recipient
- Deviations from process or conditions outside of the validated manufacturing / testing process described in the batch records or analytical test methods
- Exceeding action limits for critical process parameters
- Critical equipment Out of Calibration Results
- Findings on routine maintenance that may impact product quality. These latter may be found in unplanned work order events.
- Other major deviation events such as Environmental Monitoring results that exceed Action limits, particularly for dosage form manufacture or biotechnology APIs; potential cross contamination due to deviations from procedures or GMPs;
- Media fill failures for aseptic manufacture
- Failure in revalidation of sterilization or depyrogenation processes for equipment or components
- Trends in cleaning or sanitization activities or results that suggest that the validated process may not be in a state of control
- Rework events should be discussed with the contract giver, in general prior to initiating the work
- Frequent reprocessing events that would indicate the process may not be operating in a state of control

Quality Agreements are a documentation of responsibilities for GMP manufacture when activities including manufacture, testing, storage and distribution are outsourced. They provide clarity in responsibilities of the partners and establish lines of communication. They also clarify which of the parties has responsibility in making changes and the type of events that may need to be assessed for reportability to regulatory authorities by the contract giver or recipient. Quality Agreements should be evaluated periodically, perhaps annually, to ensure they are up to date regarding activities between the two parties. The evaluation should be documented. They are living documents, and should be treated accordingly and represent the current status of the relationship and shared activities between the parties.