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# Attention API suppliers: Quality agreements are here to stay

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**Abstract** US pharmaceutical manufacturers are increasingly requiring their active pharmaceutical ingredient (API) suppliers to sign quality agreements. This trend — if properly managed by finished-dosage manufacturers — should enable them to enhance the quality of their products without unduly burdening API suppliers. As many of these suppliers are now located in developing industrial countries, this trend will have a significant impact on global supply chains in the pharmaceutical industry. This paper, examining quality agreements from the vantage point of the contract lawyer, will discuss (1) the regulatory basis for requiring quality agreements, including recent changes prompting more finished-dosage manufacturers to require API suppliers to sign quality agreements, (2) hot-button issues in quality agreements and (3) best practices for drafting effective quality agreements. Because the authors are US lawyers, the paper is written from the perspective of US federal laws except where specific reference is made to the laws of other jurisdictions.

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## REVISED REGULATORY LANDSCAPE

The regulatory landscape for pharmaceutical manufacturers has been modified recently by additional US Food and Drug Administration (FDA) guidance that makes quality agreements much more likely to be foisted upon active pharmaceutical ingredient (API) suppliers. A bit of regulatory background is helpful to

understand the impact of this recent FDA guidance.

Section 501 of the Federal Food, Drug and Cosmetic Act of 1938 (the 'Act') has always provided that a drug not manufactured in accordance with good manufacturing practices shall be deemed to be 'adulterated'. In addition, in Parts 210 and 211 of Chapter 21 of the Code of Federal Regulations, the FDA has promulgated detailed regulations describing what is required in order to comply with the Act in this regard. Although the regulations only expressly apply to finished-dosage drug manufacturers,<sup>1</sup> FDA has long recognized that the cGMP requirements in the good manufacturing practice regulations for finished pharmaceuticals

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(21 CFR Parts 210 and 211) are valid and applicable in concept to Active Pharmaceutical Ingredient (API) manufacturing.<sup>2</sup> These regulations, entitled ‘Current Good Manufacturing Practice in Manufacturing, Processing, Packaging, or Holding of Drugs; General (Part 210) and Current Good Manufacturing Practice for Finished Pharmaceuticals (Part 211) are referred to in this paper as the “cGMP Regulations,” and the term “cGMP Regulatory Scheme”, also used in this paper, encompasses both the cGMP Regulations and the relevant provisions of the Act. API suppliers are thus required to comply with cGMP in the areas of “manufacture, processing, packing, or holding of a drug product”, which includes all packaging and labelling operations, testing, and quality control’.<sup>3</sup>

In addition to being able to rely on the FDA’s direct regulation of API suppliers to ensure their operations conform with the cGMP Regulatory Scheme, finished-dosage drug manufacturers also use contractual mechanisms to effect such compliance by their API suppliers. The most common of such mechanisms has historically been the commercial supply agreement, which typically contains a representation and warranty by the API supplier that it will produce the API in accordance with Good Manufacturing Practices or Current Good Manufacturing Practices.<sup>4</sup> Although this type of warranty technically adds no additional legal burden to the API supplier, which has a legal obligation to comply with cGMP under the cGMP Regulatory Scheme, it would provide the manufacturer with a claim for contractual damages if the supplier were to fail to comply.

Comprehensive quality agreements are essentially an extension of this warranty, providing a detailed roadmap for the manner in which the supplier will comply with the cGMP Regulatory Scheme. Until recently, it had been somewhat unusual for US finished-dosage drug manufacturers to require suppliers

to enter into comprehensive quality agreements.<sup>5</sup> That is now changing in large part due to the recent Guidance for Industry Quality Systems Approach to Pharmaceutical cGMP Regulations published by the FDA in September 2006 (the ‘Quality Guidance Document’).<sup>6</sup> The Quality Guidance Document describes its intent and goals as follows:

- This guidance is intended to help manufacturers implementing modern quality systems and risk management approaches to meet the requirements of the Agency’s good manufacturing practices (cGMP) regulations (21 CFR parts 210 and 211). The guidance describes a comprehensive quality systems (QS) model, highlighting the model’s consistency with the cGMP regulatory requirements for manufacturing human and veterinary drugs, including biological drug products. The guidance also explains how manufacturers implementing such quality systems can be in full compliance with parts 210 and 211. This guidance is not intended to place new expectations on manufacturers, nor to replace the cGMP requirements.<sup>7</sup>
- This guidance describes a comprehensive quality systems model, which, if implemented will allow manufacturers to support and sustain robust, modern quality systems that are consistent with cGMP regulations. The guidance demonstrates how and where the elements of this comprehensive model can fit within the requirements of the cGMP regulations. The inherent flexibility of the cGMP regulations should enable manufacturers to implement a quality system in a form that is appropriate for their specific operations.
- The overarching philosophy articulated in both the cGMP regulations and in robust modern quality systems is: Quality should be built into the product, and testing alone cannot be relied on to ensure product quality.<sup>8</sup>

Section IV.B.4 of the Quality Guidance Document (Control Outsourced Operations) contains the most relevant instructions concerning quality agreements. That Section provides as follows:

- Outsourcing involves hiring a second party under a contract to perform the operational processes that are part of a manufacturer's inherent responsibilities. For example, a manufacturer may hire another firm to package and label or perform cGMP regulatory training. Quality systems call for contracts (quality agreements) that clearly describe the materials, or service, quality specification responsibilities, and communication mechanisms.
- Under a quality system, the manufacturer should ensure that a contract firm is qualified before signing a contract with that firm. The contract firm's personnel should be adequately trained and monitored for performance according to their quality system, and the contract firm's and contracting manufacturer's quality standards should not conflict. It is critical in a quality system to ensure that the management of the contractor be familiar with the specific requirements of the contract. However, under cGMP requirements, the manufacturer's [Quality Unit] is responsible for approving or rejecting products or services provided under a contract (§ 211.22(a)).

The FDA has thus clearly put US finished-dosage pharmaceutical manufacturers on notice that it expects manufacturers to have quality agreements in place with API suppliers. It is therefore not surprising that US manufacturers are requiring API suppliers to sign quality agreements with an ever-increasing frequency. Based on the 'non-binding guidance' contained in the Quality Guidance Document, that trend should continue for the foreseeable future.<sup>9</sup>

## **HOT-BUTTON ISSUES IN QUALITY AGREEMENTS**

Quality agreements are generally prepared by manufacturers and provided to API suppliers, who are expected to sign them without significant changes made to them. There are, however, several subject matter areas contained in manufacturer-drafted quality agreements that should be carefully considered by API suppliers before they sign up to them. The following paragraphs highlight some of these hot-button subject matter areas.

### **Process change provisions**

Quality agreements often broadly prohibit all changes to suppliers manufacturing processes without API suppliers first obtaining the manufacturers' consent. This type of broad prohibition exceeds the legal requirements, which permit routine, non-major changes to be made without first notifying the FDA.<sup>10</sup> By unduly restricting non-major process improvements, manufacturers may substantially undermine the suppliers' ability to implement efficiency-generating and cost-saving measures that in the long run benefit both parties. For example, if the API supplier were to find a less-expensive source material containing identical chemical properties but which is a different colour, it should be able to utilise that alternative source material without obtaining the manufacturer's approval.

### **Redundant provisions**

Quality agreements are often signed where an existing commercial supply agreement is already in place or that is being signed at the same time (in the typical course of dealing, lawyers are enlisted to review and revise objectionable provisions in the commercial supply agreement, but they are not often consulted regarding quality agreements — which are sometimes viewed as an after thought). The commercial supply agreement will often contain provisions related to quality that are also contained in the quality agreement. No problem arises if the provisions are identical; however, if the

provisions differ — even only in the way they are phrased or qualified — then a conflict could arise between the documents. For example, as noted above, commercial supply agreements generally contain a warranty by the supplier that the API will be produced in accordance with cGMP — but such warranty may be qualified in some fashion, such as compliance with cGMP within the jurisdiction in which the product is being manufactured or into which it is being sold. The quality agreement would almost certainly contain a similar statement regarding cGMP compliance, but might not have the same qualification. As cGMP may differ — albeit slightly — in different jurisdictions, there could thus be a conflict between the quality agreement and the supply agreement regarding the cGMP compliance warranty.

### **The quality unit**

Quality agreements often contain express provisions that quality-related functions be performed by members of a separate ‘quality unit’. API suppliers may have certain people devoted exclusively to quality-related activities, but some such activities may be performed by individuals who also have operational responsibilities. This may be more prevalent with smaller API suppliers. Before agreeing to these types of provisions, the API supplier needs to confirm that it has segregated individuals performing the tasks in question.

### **The responsibilities matrix**

Quality agreements often contain a ‘responsibilities matrix’ containing a list of quality-related functions and adjacent to each item are two columns, one with the heading of ‘supplier’ and one with the heading of ‘manufacturer’. An ‘x’ is then placed in the column of the responsible party. There are several issues to bear in mind when reviewing such a matrix. First, the matrix may be accompanied by a narrative section that

describes each party’s responsibilities, so care should be taken to confirm that the narrative description is consistent with the responsibilities matrix. For example, if the narrative section contains certain supporting tasks for which the manufacturer is responsible, but there is no corresponding ‘x’ in the responsibilities matrix for that category, then the quality agreement could become ambiguous as to each party’s responsibilities in that area. There is also an inherent limitation in the structure of the responsibilities matrix in that it is difficult to describe situations in which there is shared responsibility. Sometimes parties agree to place an ‘x’ in each party’s column; however, that may not be appropriate when one party is responsible for most of the tasks in a given category. The ‘double x’ is particularly problematic when there is no corresponding narrative to supplement the matrix and explain which party has which responsibilities.

### **Required procedures inconsistent with suppliers standard procedures**

Quality agreements vary in their level of procedural specificity. On one end of the spectrum, the quality agreement may merely state that the supplier have procedures governing a particular area. On the other end of the spectrum, the quality agreement may set forth detailed procedures that the supplier must implement for a particular area. Detailed requirements may create issues for the API supplier. For example, the quality agreement may provide for a three-year retention period for batch records, but the supplier’s normal procedure may call for a two-year retention period. Although there may be nothing inherently unreasonable or unduly burdensome about retaining batch records for an additional year, the supplier may want to assess the long-term cost of tailoring its procedures to accommodate a single customer and its likelihood of complying with any such one-off procedural requirements.

## BEST PRACTICES FOR DRAFTING QUALITY AGREEMENTS

With the above considerations in mind, we suggest the following ‘best practices’ in drafting and negotiating good quality agreements:

- Quality agreements are legal contracts, so they should be reviewed by an individual in the organisation having contractual expertise. In addition, they should be reviewed by individuals throughout the quality organisation who have the relevant experience to assess the financial and operational impact of the agreements, which may require hiring additional quality personnel and implementing new auditing or record-keeping systems.
- Quality agreements are normally executed in connection with an executed commercial supply agreement. If there is no commercial supply agreement in place, the quality agreement should include certain legal terms and conditions normally contained in the commercial supply agreement, such as implied warranty disclaimers and limitations on damages. These types of provisions typically inure to the benefit of the performing party, so it is likely in the supplier’s best interests to seek to have them included in the quality agreement.
- Contracts are often treated as risk-shifting devices in which each party seeks to have its absolute most favourable position included in the contract, even if compliance with that provision would be very difficult for the other party. As a result, the parties often ignore the contract while performing, and the contract only becomes relevant in the future if there is a dispute between the parties. Although, as noted above, a stand-alone Quality agreement will need to contain certain essential legal terms and conditions, Quality agreements are essentially operational documents to be used by operational personnel. Therefore, they should not include provisions that a manufacturer knows the supplier will have difficulty complying with, unless the provision is essential for effective quality control. In addition to undermining the operational purpose of a quality agreement, including any non-crucial or unduly burdensome provisions in a quality agreement could cause issues with the FDA. An FDA inspector will expect the supplier to comply with the terms of the quality agreement — even any unduly burdensome terms the manufacturer knows are not essential — so the supplier’s failure to comply could possibly result in an unnecessary deficiency being noted by the FDA against the supplier. And clearly, neither party benefits when that occurs. The supplier has the hassle of responding to the unnecessary deficiency and the manufacturer jeopardises its source of supply. For all of these reasons, quality agreements should be flexibly drafted and only include detailed requirements where essential.
- If there is a commercial supply agreement in place, the quality agreement should expressly provide that it is subject to the legal terms and conditions contained in the commercial supply agreement. Furthermore, the quality agreement should contain an order of precedence clause indicating that in the event of a conflict between the commercial supply agreement and the quality agreement that the terms of the commercial supply agreement shall control. Lastly, the termination provision in the commercial supply agreement should expressly provide that a material breach of the quality agreement constitutes a material breach under the commercial supply agreement, so that it may be terminated by the finished-dosage drug manufacturer if the API supplier materially breaches the quality agreement (of course, what constitutes a ‘material breach’ of any contract is a facts and circumstances determination unless it is specifically defined in the contract).

- Strive to eliminate redundant provisions between the quality agreement and the commercial supply agreement. If overlapping provisions are identical, then one becomes superfluous; if they are not identical then a conflict between the documents may arise. One rule of thumb: if both documents are in place, the commercial supply agreement should not deal with quality at all.
- If a responsibilities matrix is used, it should specifically describe what an 'x' means and specifically define and allocate primary and secondary responsibility for joint tasks. And if the quality agreement also contains text, be mindful of any contradictions between the responsibilities matrix and the text.
- ICH Q7A is the well-recognised international standard for cGMP as applied to API suppliers. Quality agreements should therefore include that standard to maximise a supplier's ability to comply with them.

Due to the FDA's recently promulgated Quality Guidance Document, it seems API suppliers will routinely be required to sign quality agreements. This trend has likely been accelerated by the continued trend of US pharmaceutical manufacturers to go global in seeking lower cost API from places like India and China. By having quality agreements in place, manufacturers obtain enhanced contractual control over the quality control systems being used by their API suppliers in remote locations. Finished-dosage manufacturers and API suppliers will be best served by having quality agreements in place that are practical, flexible and workable. By approaching these agreements with the requisite level of care and in a spirit of cooperation, this positive result can be achieved without foisting significant additional costs on API suppliers.

### **References and Notes**

1. See 21 CFR §210.3(4), defining 'drug product' to include only 'a finished-dosage form, for example, tablet, capsule, solution, etc'.

2. Food and Drug Administration Compliance Program Manual (Program 7356.002F), dated 13th February, 2006, Chapter 56, Drug Quality Assurance at 4.
3. 21 CFR §210.3(b)(12).
4. Unless specifically defined otherwise in the commercial supply agreement, the most authoritative and widely accepted definition of Good Manufacturing Practice as applied to API suppliers is ICH Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients published by the following agencies of the US Government: Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research and ICH. This Guidance was developed within the Expert Working Group (Q7A) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). As stated by the FDA, 'ICH Q7A represents the Food and Drug Administration's (FDA's) current thinking on cGMPs for API's'. Food and Drug Administration Compliance Program Manual (Program 735.002F), dated 13th February, 2006, Chapter 56, Drug Quality Assurance at 4.
5. In Europe, on the other hand, quality agreements have been required by regulations such as Directives 2003/94 EC and 91/412/EEC, which provide that outsourced work be subjected to a written contract setting forth each party's responsibilities with respect to Good Manufacturing Practices.
6. The Quality Guidance Document was published by the following US Government agencies: Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Center for Veterinary Medicine and Office of Regulatory Affairs. Although the Quality Guidance Document states that it 'may also be useful to manufacturers of components (including active pharmaceutical ingredients)', it only directly 'applies to manufacturers of drug products (finished pharmaceuticals)'. See § II.C. (Scope of Guidance).
7. Quality Guidance Document, § I (Introduction).
8. Quality Guidance Document, § II.B. (Goal of the Guidance).
9. It should be noted that ICH Q7A also contains at least one statement urging API suppliers to use written quality agreements with their subcontractors. Section XVI of that Guidance (Contract Manufacturers (including Laboratories)) provides as follows: 'Where subcontracting is allowed, a contractor should not pass to a third party any of the work entrusted to it under the contract without the company's prior evaluation and approval of the arrangements'.
10. See Section 506A of the Act (Manufacturing Changes) and 21 CFR, Part 314.70(a) (Changes to an approved application).