Manufacturing Contracts

The manufacture of pharmaceuticals is performed by first producing active pharmaceutical ingredient and then finished product. These parts may be contracted independently at different sites, or together. For most situations, a confidentiality agreement (CDA), a business agreement, and a quality or technical agreement constitute the legal contracts between buyer and seller. The first document to be signed, a CDA, is very standard and very short. For many products, for which proprietary manufacturing information must be shared, a CDA will be needed just to obtain a proposal. The business agreement protects the rights of each party when events do not proceed as planned. The technical agreement covers the details related to cGMP manufacturing and assigns all responsibilities between the parties. Both business and technical agreements for the same manufacturing activity are needed to permit sharing the content of the technical document with regulators and thereby complying with European regulations to have a contract[1], as well as having a document that is easier to change as circumstances may require. A nuance of the business arrangements may encompass umbrella agreements and strategic or preferred partnerships and these will be briefly discussed.

Business Agreements - Confidentiality

A standard CDA should be limited in scope and bind both parties equally. While the buyer is disclosing intellectual property related to manufacturing, the contractor may also have or develop trade secrets which would preferably remain undisclosed. It is also common within a CDA to restrict both parties from making any public statements about the other without prior written authorization. The primary content of the CDA is a definition of the confidential information and a restriction on its use. To keep it simple, such information must be written and stamped or labeled "confidential". There are four standard exceptions to confidential information which must be covered in the agreement. Confidential information does not include information which

- is known to the receiving party at the time of disclosure,
- becomes public knowledge after the disclosure through no fault of the receiver,
- is received from a third party having the right of disclosure,
- is independently developed by the receiving party.

The CDA should have a limited term. While "forever" may the desire of the buyer, it is an unreasonable request. Search for some middle ground. Five to seven years is usually sufficient. The governing jurisdiction should be convenient to the buyer since he has the greater perceived risk.

Business Agreements – Standard Articles

Business agreements are organized as a series of articles, each of which contains multiple paragraphs with identifying section heads. Paragraphs that generally relate to a common thought are loosely arranged within an article to assist a reader in locating specific information more easily. However, section headings may be interpreted to limit context within a paragraph and thus one of the paragraphs may exclude headings from being a part of the Agreement. Content of a supply contract starts by defining the parties

and reciting why they are entering into an agreement. Beyond that, the first article is a set of definitions. The more things that are defined, the easier it will be to create clear intent. If the contract ever comes before a judge, there will be conflicting interpretations over content, so definitions need to be plentiful and precise.

The number and titles of the remaining articles will vary tremendously depending on which legal author wrote the first draft. However, the following discussion can serve as a guideline to the content. Every supply agreement should contain an article about "Supply and Processing", wherein one states the performance obligations of each party. Who supplies what to whom and when? Be specific, but leave some detail to the technical agreement. Phrases such as "at a time to be agreed between the parties" permit that detail to be handled by the respective corporate quality groups, while still making it clear that time constraints are intended. This article in particular should be read by a manufacturing and quality representative to assure that the company can comply with the intent. Because technical agreements have only recently gained widespread acceptance, many business agreements go into appreciable detail in areas where the legal and corporate personnel are neither qualified nor knowledgeable. For example, a common theme of the supply article relates to the amount of time that is permitted to pass from receipt of a purchase order, to the processing date, to the release of product. While such detail is of legitimate interest to the parties, it is better covered by the manufacturing and quality groups within the context of the technical agreement. If doubt exists about the ability to obtain agreement on technical or quality issues, then the technical agreement should be negotiated first.

Yet another article should explain the management of "Purchase Orders". The issue is rarely simple and may involve forecasts with minimum and maximum quantity requirements. The article can include the price to be paid for the material or service as well as the terms of payment and any price escalators for future contract years. "Shipments, Inspection, and Acceptance" will also be an article. A common defined term for shipments is Ex Works (EXW), meaning "the seller delivers when he places the goods at the disposal of the buyer at the seller's premises or another named place not cleared for export and not loaded on any collecting vehicle."[2] Such precision leaves no doubt about who bears financial responsibility for the product during the handoff. Paragraphs about inspection and acceptance should be equally precise and should be reviewed by appropriate personnel to remove redundancy with any technical agreement. Certain articles are best written by the corporate attorney. Obvious examples are "Representations and Warranties" and "Indemnities and Limitation on Liability". While rarely contentious, these are the paragraphs that bind the parties to their obligations and define financial consequences for an adverse event.

Every contract should include an article on "Term and Termination". In a pharmaceutical supply agreement, there should be a concern by the buyer that the seller may default or want out of the contract. Such concern is even greater if there is an exclusivity clause within the agreement. For the buyer to change to an alternative vendor is an expensive and time consuming adventure involving additional regulatory filings and approvals. Thus the buyer should carefully evaluate the amount of time given before

termination. For highly regulated products, one year notice of termination may be barely sufficient to locate, qualify, and obtain approval for an alternative vendor.

There are numerous miscellaneous topics that must be addressed. A reasonable list is included in Table 1. These will be drafted by the legal department and any negotiation should include the corporate attorney. Finally, most documents have a set of appendices. A minimal, but adequate, set of appendices include product identification, pricing, and timelines with milestones. The pricing appendix should address not only a commercial price, but also labor rates for miscellaneous work and re-validation work to be performed during the period of the agreement.

Table 1: The titles shown are often seen as paragraph headers in a business agreement. While legally important, they are incidental to the purpose of the agreement.

Miscellaneous Supply Agreement Paragraphs	
Title	**Description**
Independent Contractor	The parties are independent entities and not partners.
Insurance	Each party maintains its own insurance.
Governing Law	The location for adjudication.
Product Liability Insurance	Insurance to cover third party claims against the product.
Assignment	Addresses the transfer of the agreement to a third party.
Dispute Resolution	Defines the mechanics for resolving differences between the parties.
Notices	Defines where required written notices must be sent.
Waivers	Permits exceptions to the agreement under certain circumstances.
Severability	Prevents nullification of the agreement when one part is legally unenforceable.
Entire Agreement	Defines the governing agreement when other agreements may exist.
Delays or Omissions	Clarifies that lack of contractual enforcement doesn't imply a waiver.
Force Majeure	Temporarily excuses default due to acts of gods and governments.
Survival	States that certain parts of the agreement continue past termination.
Counterparts	Permit the agreement to be signed by facsimile.
Currency	Defines the unit of currency – usually the US dollar or Euro.

Business Agreements – Clinical Supply, Phase I and II

Manufacturing new chemical entities implies development by both parties. Milestones will be set, but unrealized timing expectations for development have led to the demise of more than one organization. In addition to process development, the manufacturer must also acquire expertise in new test methods. He will most likely lack exact specifications and it is worth noting that non-validated processes in both production and the lab may lead to ambiguous results. Timing issues throughout the contract must be carefully reviewed to assure the ability to perform. Agreements predicated to supply early phase trials may be best cast to pay for effort rather than results. Change orders are likely and need to be addressed in the agreement. Additionally, one might expect low yields for early phase manufacturing. Price clauses may use novel units. For example the buyer might purchase a batch of material rather than a specified number of grams or units. These agreements will contain all of the standard articles previously discussed, but the principle articles will differ significantly in content. While termed "clinical supply agreements", the need for validation and specification development suggests an agreement that focuses more on development service than simple material supply.

Business Agreements – Phase III and Commercial Supply

Within FDA, phase III clinical trials, are expected to be performed with materials that have been produced exactly the way that post-approval material will be produced. Such conditions are most easily met by manufacturing the phase III materials at the same site and perhaps with the exact equipment to be used for commercial manufacturing. That decision is both economical and practical. After the phase III materials are made, the testing methods have been validated, and the process is very close to being defined. At that point, a buyer can expect to obtain pricing for delivering fixed numbers of grams, tablets, or vials because the manufacturer has experience with the production process. In the commercial supply agreement, the process is well defined and can be referenced from the definition of the "Master Batch Record". Still, the final process validation will not have occurred and sometimes will not occur until post approval. Prior to validation, the agreement should make clear what risks exist and to whom those risks are assigned. For example, if the buyer is supplying an active ingredient for manufacture into a finished dosage form, then the contract may discuss consequences for failure to maintain yield. Clearly in that situation, the agreement should specify what actions are to be taken, both financial and otherwise, in the event that the yield specification is not met. Such action can be different before and after process validation. During start up of manufacturing for commercial supply, unexpected events are more likely than at a later time when the manufacturer has more experience with the product. Similarly, there may be circumstances that require an investigation before batch release and those circumstances may result in the manufacturer being unable to meet timely delivery obligations. Except for instances of malfeasance, contractual consequences should be something other than default. When the only contractual consequence of an adverse event is default, then the contract has failed and both parties are dissatisfied.

Technical Agreements

Also termed a "Quality Agreement", this document is a requirement of the MCA and commonly used throughout the industry. As a stand alone agreement, it can be shown to regulatory authorities as evidence of compliance, whereas the business agreements are not available to regulatory scrutiny. Primary concerns of the agreement are to assure that all cGMP requirements are met, to assign responsibility between the parties for the individual tasks, and to ensure that product for sale complies with any approved product application. Communication is a key issue in the document. Who, what, when, where, and how make up the detail. Substantive articles are listed in Table 2, which is not intended to be exhaustive. Any detail that involves specific actions needed to obtain quality assurance release of product and may need to occur with specified timing, but is not a specific batch record instruction, can be appropriately addressed in the quality agreement. While not an explicit requirement of US cGMP, it is prudent to have a technical agreement to accompany every business agreement.

Table 2: Primary article headings that might be seen in a Quality Agreement.

Quality Agreement Articles	
Title	**Description**
Responsibility Matrix	Assigns cGMP responsibilities to a specific company.
Documents	Defines those documents that each party must produce.
Change Management	Addresses planned and unplanned changes, deviations, and variances.
Regulatory Audits	Actions required for internal, inter-company, and governmental audits.
Testing and Specifications	Addresses the consequence of testing for release, shelf life, and export.
Recalls and Complaints	Defines the actions necessary to accommodate a recall or customer complaint.
Subcontracting	Permits certain items to be subcontracted by the manufacturer.
Key Events	Requires mutual notification for major events which could effect the product.
Investigations	Defines actions and responsibilities and timing requirements.
Review and Release	Defines who has to sign documents and by what deadlines.
Validation/Re-Validation	Addresses the need and repeat frequency
Annual Product Review	Specifies what must be done, by whom, and when.

Corporate Counsel

Corporate attorneys may get involved in all of the activities described and they are rarely experienced in the nuances of pharmaceutical, GMP, supply. Consequently,

their allotted time for contracts is probably better used in drafting standard business paragraphs and providing guidance policy about what can and can't be changed. Overall, attorneys assist companies in negotiating adverse events. By obtaining advice before an agreement is signed, one can sometimes avoid adversity.

Strategic Partnerships

Companies form alliances for specific purposes and mutual benefit. In a strategic supply agreement, the benefit to the buyer is probably quantity discount pricing and preferred customer scheduling. There is also a comfort factor associated with preferred partnership arrangements which cause a buyer to seek additional product manufacturing from the preferred partner. The benefit to the seller is guaranteed business, exclusive manufacturing rights, and probably a longer term contract. The strategic supply document is likely to have all of the provisions already discussed for supply agreements, but may be changed in the definition of "product" and may even defer that definition to appendices and technical agreements. A careful business contract, termed an umbrella agreement, can be written that does not require change in order to add new products. In most cases, a separate technical agreement will accompany each product, since there are many product specific details that must be addressed. By having a single business contract, much time and energy can be saved as multiple products are carried through the system and quality teams from the two companies capitalize on prior communication and acquaintance.

Royalty Based Agreements and Licensing Fees

Intellectual property (IP) agreements are beyond the scope of this article. However, IP holders who license their marketing rights, but retain manufacturing rights, use supply contracts similar to the ones discussed above. Often, some portion of IP manufacturing compensation is from royalties based on sales of their product. Such sales are likely to earn different royalty amounts over different periods of time and from sales in separate markets. A significant additional article in the business agreement, titled "royalty payments" is needed to administer the terms under which royalty sales are earned and paid. The new arrangement may even include a financial audit or the required use of sophisticated software to track complicated royalty compensation. Rarely, would a contract manufacturer, who is not an IP holder, accept a royalty arrangement as partial compensation for the manufacturing effort. That would constitute a financial investment by the contractor. Start up risks for pharmaceutical products are high and those risks are not assumed by a contractor in the context of a supply agreement.

Summary

The essential elements of a manufacturing supply agreement have been reviewed, along with the accompanying quality agreement. They differ in that the business agreement is meant to define the legal obligations and consequences of an adverse event, while the quality agreement is a working document that enables the companies to manufacture and sell product that meets regulatory requirements. The two documents are

complementary and mutually beneficial when the business agreement recognizes in advance the content and strengths of the quality agreement.

References

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