Preparing Requests for Quotations
For Commercial Pharmaceutical Manufacturing

George F. Klein

With the increase in pharmaceutical outsourcing, preparing requests for quotations (RFQs) has become more important than ever. This article presents a procedure for writing RFQs for commercial manufacturing. It will enable you to write a document suitable for bidding by contract manufacturing organizations (CMOs). The method can be used for the outsourcing of existing oral dosage forms or new products. It can be adapted easily to obtain quotes for active pharmaceutical ingredient (API) manufacturing or for parenteral production.

Before writing an RFQ
Before beginning to write an RFQ, a few topics must be addressed. A bidders list must be developed. Once a list has been put together, confidentiality agreements must be established with the selected CMOs to protect your proprietary information given to them as part of the RFQ.

To decide on a CMO, pharmaceutical business publications should be consulted. Trade shows provide another excellent way to meet prospective bidders. Perhaps the best method is through associates in the industry who have had previous experience in contracting out pharmaceutical manufacturing. Don’t neglect big pharma when developing a bidders list. My past experience indicates that they may be higher in price than companies that obtain most of their revenue from contract work. However, the quality of big pharma’s work is usually excellent.

Before sending the RFQ to the bidders list, you may wish to contact each CMO’s business development department. Introduce yourself to the company. Explain the manufacturing that you would like them to bid on, leaving out any confidential information. Assess their interest. If your firm has a Web site, let the business development representative know the address. Web sites build credibility, especially for start-up or virtual companies. You also may want to arrange a visit to their manufacturing facility after you have sent them the RFQ.

Before issuing the RFQ, a confidentiality agreement must be established between your company and the CMO. This will protect your company’s proprietary knowledge that is submitted to the CMO in the RFQ. The confidentiality agreement is a legal document and must be reviewed by your corporation’s counsel. Other people involved in the review of the confidentiality agreement could be personnel from the manufacturing, formulations,
Outsourcing Resources

purchasing, business development, and fi-
nance departments.

Two items on the confidentiality agree-
ment often are overlooked: First, many
standard agreements apply for three years.
I recommend that the confidentiality agree-
ment be extended to five to seven years to
protect your proprietary knowledge for as
long as possible. Second, if yours is a start-
up or virtual company and is not showing
a profit, you may wish to have the confi-
dentiality agreement governed by the laws
of your state or region rather than the state
or region of the CMO. Should legal actions
occur because of an alleged breach of the
agreement, travel to the CMO’s area for
legal proceedings could be expensive. These
expenses would become an excessive bur-
den for a company that has no consider-
able revenue source.

Writing an RFQ
A basic outline for an RFQ is as follows:

- introduction
- manufacturing volumes and schedule
- manufacturing requirements
- quality control requirements
- validation requirements
- stability
- supplied to the contractor
- appendix.

These are the major sections of an RFQ. Each is discussed below in greater detail.

Introduction
This section, though short, serves to in-
troduce the product to the CMO. Here,
you may include a brief description about
the product, providing its chemical name
and its indications. Provide status of its
approval process with FDA (e.g., “the pro-
don’t recently completed Phase III clin-
ical trials”). Ask the CMO to attach its
standard terms and conditions to its pro-
posal. State that any deviations from the
conditions in an RFQ are to be highlighted
clearly in the CMO’s proposal.

Manufacturing volumes
and schedule
This section and the following two sections
(manufacturing requirements and quality
control requirements) are the heart of an
RFQ. In the manufacturing volumes and
schedule section, provide anticipated vol-
umes and delivery dates on a monthly or
quarterly basis during the term of the con-
tract. Volumes should be given in number
of tablets or capsules or liters or kilograms
if the product is a liquid or a semisolid. Also
list stock-keeping unit (SKU) volumes (i.e.,
the number of bottles of each package style
that should be delivered). For liquid or semi-
solid products, you could specify an over-
fill so that all CMOs will quote on the same
number of bottles. Overfill amounts vary
with the type of filling equipment used, so
they may vary from CMO to CMO. By speci-
ifying an overfill, all contractors are bidding
on an even basis.

If you are writing an RFQ for the out-
sourcing of a marketed product, produc-
tion volumes most likely will be well
known. But for new products, production
volumes are not as firm. This point is im-
portant because most CMOs may insist on
penalties if projected volumes are not met.
Between receipt of bids and contract sign-
ing, manufacturing projections might
change, especially for new products. A note
should be added to the RFQ stating “vol-
ume demands shown are projections and
actual volumes will be fixed at contract
signing.” Basically, this section is a manu-
facturing schedule. It could be structured
as shown in Table I.

<table>
<thead>
<tr>
<th>Year</th>
<th>Deliverable Date</th>
<th>Deliverable Amount</th>
<th>Deliverable Packaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>01 April</td>
<td>10,000,000 tablets</td>
<td>60,000 bottles of 100s in a 2-oz HDPE bottle with heat induction seal, cotton, and child-resistant closure.</td>
</tr>
<tr>
<td></td>
<td>01 July</td>
<td>10,000,000 tablets</td>
<td>60,000 bottles of 100s, etc.</td>
</tr>
</tbody>
</table>

Manufacturing requirements
This section can be set up in a numbered-
otes format, with all your manufactur-
ing requirements listed in detail. Num-ery each item will make this section
clearer for the CMO and easier during bid
analysis if the CMO has any objections,
reservations, or suggestions for improve-
ments about any of the requirements. In
this section, the following is detailed:

- Specifications on the packaging to be
  used (e.g., bottles, blisters, dosing cups).
- For bottles, include vendor drawings of
  the selected bottle and cap designs.
- Warehousing and shipping destinations
  of the final drug product.
- Cartoning, labeling, package inserts, and
  bottle sealing. If labeling and inserts are
  not decided upon at the time of the
  RFQ, have the CMO quote a standard
  label and insert.
- How pricing is to be specified by the
  CMO. That is, should the pricing include
  all costs (e.g., $/SKU) or be broken down
to show fixed and variable costs? It is
best to specify how you want the pric-
ing done for your product. Reviewing
the bids will be easier if all of the costs
are on the same basis.
- If your corporation will supply the API,
  state so. If not, include the address of the
  supplier and cost information. Either
way, it’s best to include a material safety
data sheet (MSDS). Note any unusual
safety or hazard issues (e.g., “the API is
highly toxic”).
- For unusual or atypical pharmaceutical
  excipients, include some of the manu-
facterer’s information such as specifi-
cations or a typical certificate of analy-
is. Also include pricing information and
an MSDS.
- If you have any specific project man-
  agement requirements, list them in this
section. Always insist on a project man-
ger. Contract manufacturing involves
many departments (e.g., validation,
quality control, manufacturing, and ma-
terials management). It is best to have
one person, the project manager, who
directs communication and one person
who is accountable for your project.
- The CMO is to write a master batch
  record for both the bulk drug product
  manufacture and the packaging.
- Request pricing for change parts for pro-
cessing equipment, tablet presses, packaging equipment, etc. Ask for an itemized list and note that the parts are to be turned over to your company at contract termination. New change parts can be expensive, often costing well over $100,000. A way to save on packaging-line change parts is to evaluate the type of bottles that can be filled by the CMO. It is possible that the CMO may not be able to run your selected bottle or cap but could run something similar. If so, it could be worthwhile to change to the compatible packaging. Discuss this possibility with the contractors during the bidding process. Stability is required before product launch, so most likely there would be no additional expenses to obtaining stability data for packaging that is compatible with the CMO’s equipment.

- Note that raw materials and packaging supplies should be sourced from approved vendors only.

- Information about the manufacturing equipment should be provided so that the CMO has an idea of the adequacy of its equipment. If special process machinery is required, state so. If you wish the CMO to guarantee equipment performance on your process or if you wish to verify its suitability, then also note it here. This would be a good place to state any special materials-of-construction requirements, hold time restrictions, instrumentation, data logging and analysis, or production area particulate classification.

- CMOs may at times subcontract their work. If you find this objectionable, note it in this section or ask the CMO if it intends to subcontract any work and request information about the subcontractor. You may at some point during the bidding process wish to audit the subcontractor.

- A preapproval inspection (PAI) will, of course, be conducted by FDA. The CMO should include costs associated with the PAI in its bid and costs for you or a representative to perform PAI rehearsals.

- Cover any other special safety or environmental issues with the product.

**Quality control requirements**

This section specifies what will be required of the CMO’s quality control department during commercial manufacturing. Quality control–related functions such as stability and validation are covered in the “Stability” and “Validation requirements” sections.

This section also can be formatted in numbered notes, similar to the manufacturing requirements section. Most important in this section is to include the product release and, at least, proposed stability specifications. Include copies of any analytical methods for product testing. If you require the CMO to develop any analytical methods, state so. Include any information that may be helpful to them to accurately assess these development costs.

If the CMO is well established, it should have validated analytical methods available for the most common pharmaceutical excipients. If your product contains an atypical excipient, the CMO must develop release-testing methods. Ask that the contractor company include the cost for such work in its proposal, if necessary.

The numbered notes should include the following:

- Explain the in-process testing that is required for the drug product.
- Note that batches are to be manufactured and tested in accordance with good manufacturing practices (GMPs) and good laboratory practices. Routine auditing by the CMO’s quality assurance staff should be conducted on batch and laboratory records and in production and laboratory work areas per GMPs.
- The CMO is to perform release testing on all raw materials. If you have an objection to using reduced testing protocols, state so. I recommend using reduced testing for qualified vendors of common excipients because of the cost savings. The CMO should source typical raw materials only from approved vendors. Recommend that the contractor use US Pharmacopeia methods where appropriate. In some cases, you may wish to perform release testing on your API. If so, note it in this section of the RFQ.
- The CMO is to perform all release testing for the drug product. You may wish to include the analytical methods for release testing, if they have been developed.
- Retain samples should be maintained of drug product batches, per GMPs.
- Reserve the right to modify the CMO’s excipient specifications. After contract signing, request a copy of the contractor’s specifications for review. Review and make changes where appropriate and request that the CMO notify you about any cost changes resulting from the review. Alternately, the specification review could be done before contract signing, although this tends to add more confusion to an already complicated process. In the vast majority of cases, CMO excipient specifications are adequate and well written.

- CMOs may at times subcontract their laboratory work. If you find this objectionable, note it in this section or ask the CMO if they intend to subcontract any work and request information about the subcontractor. You may at some point during the bidding process wish to audit the subcontractor.

- Other quality issues can be covered by contract clauses, or, as is popular presently, a separate quality contract with the CMO. I recommend that the selected CMO be audited immediately before contract award. The auditor will undoubtedly have observations on quality SOPs. These procedures should be evaluated, and clauses should be added to the contract on these issues.

**Validation requirements**

The following four subsections should be included in this section:

- process validation
- cleaning validation
- installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ)
- analytical validation.

**Process validation.** The CMO must conduct a full process validation, including the following:

- protocol writing
- manufacture of three validation batches
- testing of the validation batches per the protocol
- validation report writing
- validation batches stability monitoring and stability report.

Usually, the CMO should write the process validation protocol even if the process involves new technology or esoteric processing techniques. If your company writes the protocol, it may give FDA the impression that the CMO lacks this
basic skill. Your corporation’s technical staff still may be behind most of this document, though. Of course, you should have the final approval of the process validation protocol.

To provide a common basis for quotation for an RFQ, you may wish to specify how the validation is to be performed or include a sample protocol. Conversely, you could let the CMOs quote on their standard protocol. However, to avoid complications, it is best to provide a sample process validation protocol.

The “Stability” section discusses the stability testing requirements for validation batches.

Cleaning validation. Typically, during clinical trials manufacturing, cleaning methods and validation are not developed, or only limited cleaning verification has been performed. Therefore, the CMO must be relied upon to develop and implement these methods during commercial manufacturing. Should it be known or suspected that the API is difficult to clean, note it in the RFQ. A highly toxic API or an API with a low aqueous solubility most likely would fall into this category.

If any work has been performed on cleaning methods or validation, it would be best to state it in the RFQ. Upon selection of a low bidder or bidders, the information could be transmitted to them so a firm cost for cleaning validation development can be determined.

For commercial manufacturing quotations, some work on cleaning validation most likely would have been performed after the manufacture of the Phase III clinical supplies. If so, include or summarize the work in the RFQ. However, it is probable that the bidding CMOs will have to modify or even supplant the previous methods. Each CMO will have different methods for cleaning as well as different equipment and other infrastructures that may not permit transfer of the previous cleaning procedures. What was developed in Phase III may have only limited applications if a different contractor is selected for commercial manufacturing. Ask the CMO to review and comment on the submitted procedures when the timing is appropriate.

IQ/OQ/PQ. The contractor should include any costs associated with the IQ/OQ/PQ of any new equipment required for your project. Remember that IQ/OQ/PQ applies for both process and analytical equipment.

For process equipment, require that the IQ/OQ/PQ work be completed before the start of process validation and that the IQ/OQ/PQ reports are ready for the PAI. Note that you must review and comment on these documents before the PAI.

If existing equipment is used, as it will be in most cases, ask to review the IQ/OQ/PQ reports before the PAI to be sure of their adequacy.

Analytical validation. Here, note that you will supply the CMO with validated analytical methods for release of the API and/or the drug product. Or, conversely, you may wish to have the CMO quote the price of the development of the necessary methods.
If you will supply the contractor with the analytical methods, ask the contractor to review the methods for adequacy in its facility. Request that the company quote prices to transfer the methods to its facility. Any crossover study reports and validation or revalidation reports must be available for the PAI.

**Stability**

In this section, stability requirements for process validation and commercial manufacturing are covered. A sample stability protocol could be provided. State that International Conference on Harmonization guidelines for stability testing are to be followed.

Usually, validation batches are placed on both accelerated and controlled-room temperature (CRT) stability. Marketed batches that are placed on routine stability monitoring (GMPs require a minimum of one batch a year on stability) are usually only CRT.

During commercial manufacturing, operational difficulties or errors sometimes occur. The CMO’s (or your company’s) quality control department may find it necessary to place the affected batch on stability. This could be an accelerated study for three months before release or concurrent CRT stability. The RFQ should state that the CMO must bear the cost of any batches placed on stability as a result of its induced operational difficulties or errors. Reserve the right to override its quality control department if it thinks stability is unnecessary on such problem batches.

The following schedule is usually acceptable practice for the stability report on the validation or marketed batches:
- issued after three-month accelerated data are obtained
- issued after six-month accelerated and room temperature data are obtained
- at the end of 12 months
- then annually thereafter, usually to three years or expected expiry.

**Supplied to the contractor**

The following items are given to the CMO after contract signing:
- Phase III master batch records
- analytical methods, if applicable
- reference standards
- cleaning procedures, if applicable
- API specifications and certificates of analysis
- raw material specifications, if applicable.

**Appendix**

In this section, documents such as a process-flow diagram, process validation protocol, the formula, specifications, MSDSs, and the stability protocol are provided.

Finally, don’t forget to stamp the RFQ and all attachments “Confidential.”

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