
GEMINI PHARMACEUTICALS

## Manufacturing Perspective:

# What to Look for in a High - Quality Contract Manufacturer

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This whitepaper will provide a basic overview of how to assess the quality of the Contract Manufacturing Organization (CMO). Industry is bombarded with confusing and sometimes conflicting information about this issue, i.e. value of a 3rd Party audit/registration by a recognized group, the need to actually visit your CMO, the structure of a Quality Agreement, industry reputation of CMO and other points. All of which ultimately provide the framework for the quality of your products. However, a misunderstanding or overreliance on any of these may not be sufficient to guarantee the quality of your products, and also might leave large gaps which bring tremendous risk to your entire business.

## *3rd Party cGMP Registrations*


We will first take a look first at the 3rd Party cGMP registrations. Are they sufficient to entrust your business to a CMO? The answer is NO - but they are a good start. Media has reported several high-profile instances of manufacturing operations that had a current independent 3rd Party cGMP registration, yet their FDA audit all ended with both 483 observations and publicized Warning Letters. A 3rd Party cGMP registration only provides a snapshot of the CMOs compliance to cGMPs. Realistically the 3rd Party auditor may be at the facility for only a couple of days, where an FDA audit may be focused, last weeks, and have multiple auditors present. So the good news about a 3rd Party registration to cGMPs means the CMO is willing to open their facility up to scrutiny by an outside party and are willing to pay to have it done. Do the 3rd Party audits help the CMO point out areas of non-compliance and help the CMO improve their overall quality program? The answer is a qualified YES, but it also depends on the thoroughness of the auditor and the willingness of the CMO to make recommended changes. Are all

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3rd Party registrations the same since they are all essentially auditing to the same 21CFR document? Sadly the answer is NO again but that is topic for another article in itself.

## ***Quality Questionnaire***

Looking for a CMO that has a 3rd Party registration should be the minimum acceptance criteria before proceeding any further, as the presence of or lack of that relationship is important. The next step in this process is a detailed manufacturing and quality questionnaire. When agreed-upon, it should be signed by the person directly responsible for the quality assurance of the products made by the CMO or by the CEO. Obvious “Red flags” would be too many “No”, “Pending” and “N/A” responses. This document is a living and breathing guide to the relationship, and cannot simply be filed away. It must form the basis of the next critical step in evaluating a CMO – The Onsite Audit.

## ***Onsite Audit***

This is by far the most overlooked, time-consuming, expensive and pushed-off step in the whole CMO qualification process. All too often the Brand Owner/ Own Label Distributor will not proceed to this

crucial step once the CMO has a 3rd Party Registration and signs the QA questionnaire – why then bother with an audit? However, do not skimp on this step. Take the time to thoroughly investigate the CMO and their commitment to making quality products for you. Whether your QA team does the audit or you hire a consultant to do it – Get it done **before** placing the first order!.

This audit needs to go beyond a "visit/tour" where everyone shows up in the morning, tours the plant, has lunch, looks at a few SOPs, and catches the afternoon flight home. This audit needs to be a complete dissection of the CMO and how they manage the quality program. It will probably take 16 to 24 hours for the initial audit with considerable follow up to that audit and subsequent visits in order to have an understanding of the CMO's quality system

Don't be taken in by a nice lobby and everyone walking around in lab coats and hairnets. Some suggestions are below, but this is by no means complete -

- Have an audit checklist prepared. Use the signed Questionnaire to help guide the audit.
- Tour the facility when you first arrive. Make notes to follow up on later rather than getting bogged down.
- Have access to 21CFR Part 111 during the audit and refer to it as necessary.
- Review every SOP. Make sure they aren't missing critical ones.
- Review to the training files for, at least, all QA personnel and the escort team.
- Ask to see a complete batch record for a product similar to the one they will make for you. (Let them redact the client's name and product but nothing else, unless there is a proprietary ingredient in the formula).

- Identity testing – Has it been done and are they using a reference material with a scientifically valid method?
- Are the raw material vendors qualified?
- Contaminate testing on raw materials?
- Raw material specifications signed off by both parties?
- A Master Manufacturing document for that material and lot size?
- Weighing documents signed by 2 people?
- Finished product specifications?
- Finished product testing – is it designed to meet 100% of label claim? Does it?

- Lastly, ask to take another tour of the facility and talk to the people on the floor who can have a direct impact on the quality of the product being made. Do they know the relevant SOPs? Have they been trained on the SOPs? Do they have easy access to the SOPs related to their job function?

If you are not comfortable with what you observed, or the CMO will not make the suggested corrective actions, do not accept them as your CMO. It is far better to start the whole process over with another CMO – it's your business you are putting at risk so choose wisely.

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## ***Agreements***

Based on your finding the CMO acceptable, a Quality Agreement needs to be put in place outlining who is responsible each aspect of product quality. Do not overlook or bypass this step. There are numerous examples of this document available on the web.

Depending on the amount of work the CMO will be doing for you, you may wish to consider a Supply Agreement also. This is more of contractual document but quality aspects can be woven into it as well.

***One requirement that has to be in one of the documents is the CMO will provide you with complete batch records for every lot of material produced. You may want to broach this subject with them even before you send the Manufacturing Questionnaire. CMOs historically have not wanted to provide this documentation. If they aren't willingly do this, then don't even start the process with them – Go to another CMO.***

If all of the above is completed successfully, now you are ready to place an order – But your job is not done yet!

## ***Partnership/Transparency***

Now comes the integration of their quality procedures and SOPs with yours. Have SOPs in place for all of the Quality Aspects (21CFR Part 111) that you are held accountable for once the product is delivered to you. Make sure everything is seamless for a smooth hand off.

Observe the first lot or two of your product being made from start to finish. Is everything being done as outlined in the Questionnaire, the SOPs, and your audit? Have they provided you training on how to read and interpret their batch records?

Selecting and qualifying a CMO is not an easy task and should not be taken lightly. It is also not going to be inexpensive to do. You now have time and money invested but so does the CMO if they are doing things correctly. High quality products come with a price, so the lowest cost CMO may not be the best partner for you.

If you have a CMO doing work for you and the above steps have not been taken or some of the steps were missed, correct this oversight as soon as possible. You may find your current CMO is not who or what you thought they were. Don't stick your head in the sand – change the CMO.

**Please never lose sight of the fact it's your business and your reputation at risk - not theirs. If there is a product recall or an FDA Warning letter issued to you, it will cost you a lot more money to fix the problem after it happens than taking the basic precautions outlined above and selecting the right CMO as your partner.**

For more information, please visit www.geminipharm.com