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WHITE PAPER

Choosing a Contract Development and Manufacturing Organization (CDMO)

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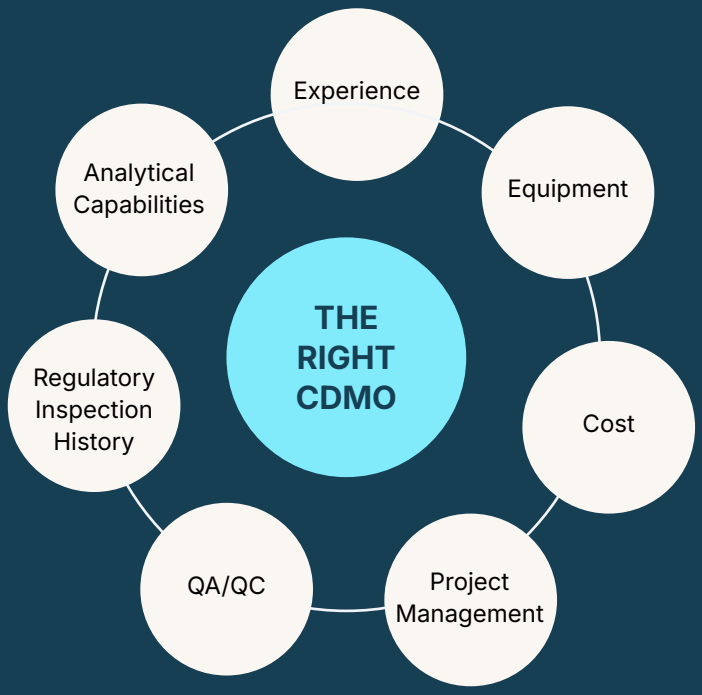
When choosing a CDMO to work on a project, there are a number of important areas to consider prior to making a selection. Often, the formulation experience within the group and the available equipment are main drivers for the selection process, with the cost, timeline, level of experience with what needs to be done in the project, analytical capabilities, and regulatory inspection track record of the site being important factors as well. These additional areas should be examined as part of the due diligence process to ensure the drug product CDMO selected is the best fit for the project. Further considerations include the phase of development the project is in, the clinical need for the product, and the sponsoring company's overall objective.

These aspects, along with those covered below, should give a holistic view of the project and help to guide the selection of a CDMO that will be a good partner.

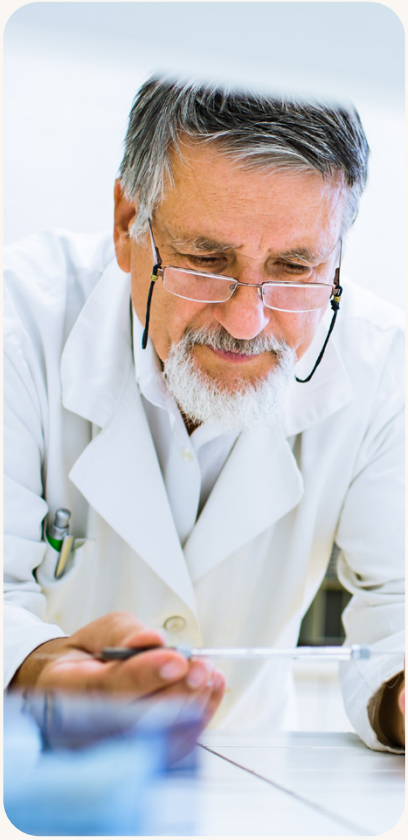


Formulation Development and Process Design

Beginning with the aforementioned formulators, the resources available within this function are critical.

A few key questions that need to be considered are these:

- **What is the experience level of the internal and external team members?** Some sponsors may or may not have internal expertise for all necessary CMC areas that will come up over the course of the project. Making sure the CDMO has expertise in these areas can help fill any gaps that may exist in internal knowledge bases.
- **Will the project team include representatives of other functions (formulation, analytical, QA, QC, project management, etc.) right from the outset?**
- **How many other projects is this team supporting currently?** Can they support an additional project?



Another consideration is whether there is a need for analytical methods transfer or will new methods need to be developed and eventually validated? The analytical group at the CDMO being considered should have an analyst-to-formulator ratio of at least 2:1 to handle project work in a timely fashion. This is especially important when a project is in early development and a lot of analytical support is needed to analyze blend uniformity, content uniformity, DOE, or stability samples. This can be a huge strain on laboratory resources, and the group's ability to handle these situations should be scrutinized. A well-staffed analytical group with sufficient instrumentation should be near the top of any list of requirements for CDMO selection.

Below is a list of questions that need to be considered when examining the analytical capabilities of a CDMO during the initial selection process.

- **Is the CDMO staffed appropriately in the analytical group to support the project?**
- **Will the CDMO have an analytical lead dedicated to the project who will provide continuity during the entire time the project is at the CDMO?**
- **Are cleaning methods readily available that can be transferred to the CDMO or will these methods need to be developed?**
- **Is information available to calculate cleaning limits?**
- **How quickly can cleaning work begin once the project is initiated?**
- **Are methods available for assay, related substances, dissolution, etc., that can be transferred or will they need to be developed?**
- **Does the CDMO have all the necessary instrumentation to support all development work?**
- **Is analytical instrumentation dedicated to development projects or shared with QC to support commercial product release testing?**
- **What stability storage conditions can be accommodated?**
- **What is the capacity of the stability equipment?**

General Capabilities and Resources

With the formulation and analytical aspects addressed, other considerations are based on the phase of the project. There are different aspects to consider for a project in the preclinical stage as opposed to Phase III. For instance, for a preclinical project, what does the CDMO have in the way of benchtop equipment? Can batch sizes on the gram scale be handled when NCE availability and cost are major concerns? If the project is a Phase III tech transfer, the CDMO will need to have similar equipment trains to those used at the originating manufacturing site.

Are you searching for a CDMO that can take a project from inception to commercial?

This presents a different set of capabilities to examine. In addition to the benchtop equipment that will be needed for preclinical work, scale-up capabilities should also be examined. A company must be able to transition the product between scales as seamlessly as possible. Usually, that means having equipment of the same, or similar, design at multiple scales. A typical development project may start with gram-scale batches, increase to single kilogram batches for Phase I supplies, tens of kilograms for Phase II, and maybe up to 100 kilograms for Phase III supplies. The CDMO needs to have equipment trains on hand to handle these scale transitions. It is easy to overlook some of these aspects, especially early on in a project when formulations and manufacturing processes are largely unknown.

There are a few main process trains that could be areas of focus. For example, common equipment to make a solid oral dosage form might include blenders, mills, granulators, fluid beds, tablet presses, encapsulators, dedusters, polishers, weight checkers, pan coaters, printing equipment, etc. If the product needs enabled formulation due to, for example, solubility issues, equipment for spray-dried dispersions (SDD), hot-melt extrusion (HME), or nanosuspensions will also be needed. Having equipment trains to handle these processing steps at different scales will be a requirement. If there are gaps, a discussion about how those gaps could be filled should take place. For example, if there is a blender size gap once the project gets to Phase III, would the CDMO be willing to initiate a purchase for that blender upstream in the project lifecycle so that by the time it's needed, it has been received, installed, and qualified? Would it be mutually beneficial for the sponsor company and CDMO to share the costs related to such activities?

The table below lists some additional high-level considerations to inquire about during the selection process.

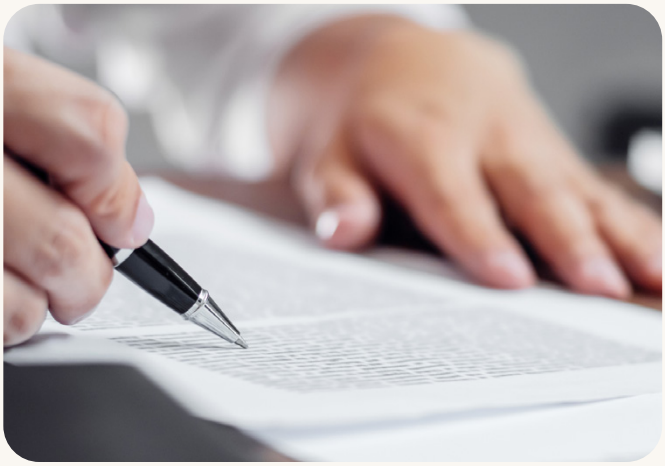
	Preclinical		
High-Level Considerations	**Phase 1**	**Phase 2**	**Phase 3**
Preformulation capabilities	✔		
Benchtop equipment availability	✔		
Rapid formulation prototyping	✔		
Flexible and efficient Quality Management System	✔	✔	
Complete and analytical method validation			✔
Fully validated equipment			✔
DSCSA compliance (serialization and eventually aggregation)			✔
Scalability of equipment trains	✔	✔	✔
Analytical support capacity	✔	✔	✔
Cleaning methods available	✔	✔	✔
High potency containment availability	✔	✔	✔
Active and engaged Project Management	✔	✔	✔
Packaging and labeling capabilities to suit project needs	✔	✔	✔

High Potency Capabilities

API potency can bring additional challenges. If the API is highly potent, specific questions will need to be asked of the CDMO to ensure that the molecule can be safely handled at the site. Given the categorization (such as those provided through SafeBridge, Affygility, or another reputable toxicology firm), the CDMO may need to have engineering and other controls in place to ensure their personnel are safe and the API will not pose a cross-contamination hazard in their facility.

- **Does the facility have a high potency processing area?**
- **Is appropriate containment in place in manufacturing spaces and analytical laboratories?**
- **Is equipment shared between high potency and non-high potency areas? If not, what equipment trains are available that are specific to high potency processing?**

Many times, during early development, OEL (Occupational Exposure Limit) and/or PDE (Permitted Daily Exposure) are unknown. For that reason, a CDMO may place the API in question into a default category so it is treated as a highly potent material until enough safety/toxicology information has been generated to potentially recategorize it to a lower (safer to handle) band. If this happens, generally there will be a higher cost associated with these activities due to the extra steps needed to ensure safety and containment.



An additional layer of complexity is added to this subject when it comes to classification systems. Companies such as SafeBridge and Affygility have their own classification systems. On top of this, each CDMO has developed a classification system that may or may not be the same. For example, one company's classification system may be based on a 1-5 banding while another may have the same banding but split their band 3 into a 3A and 3B, each with different criteria in terms of what controls must be in place to handle the material. Material classification should be discussed early in negotiations with a CDMO so additional time and costs can be accurately determined and accounted for.

Other Essential Functions and Project Support

Project Management

The CDMO's internal team and how it will interact with your team is another consideration in the selection of a CDMO for the project. Frequency and pace of communication are other factors that should be discussed prior to the initiation of a project. It is important that SMEs are available to "talk shop" on an ad-hoc basis outside the established team meeting cadence. The CDMO should also have a strong project management function. Meetings should be set up on a weekly or biweekly basis as needed. The CDMO should be flexible around this and willing to adjust meeting frequency as project demands dictate, allowing for more frequent meetings during critical stages of development and less frequent meetings otherwise. Also, given the nature of development and the changes that will occur during the program, the CDMO should be flexible with scheduling time for manufacturing activities both in development areas and in GMP suites. This flexibility will be key to meeting timelines and keeping the program on track.

Quality Systems

Built-in flexibility and efficiencies in a CDMO's Quality Management System is another important area of examination during the due diligence process. A strong quality culture with a successful inspection history are important factors when selecting a CDMO. At the same time, there should be systems in place for risk-based and phase-appropriate application of quality/compliance requirements to allow for efficient progress early in development where many changes occur and the need to be nimble exists. Additionally, the client may not have an internal QMS, and should be able to leverage the CDMO's systems during early development. For example, in the CDMO's quality system, it should be acceptable to simply have a fit-for-purpose method in place to analyze excipient compatibility samples during preformulation characterization studies. Then, as the project progresses into clinical stages, requirements become increasingly more stringent, leading up to full validation during Phase III activities. Having the ability to handle the tight timelines and many changes that will occur in the early stages of a project are necessary characteristics of a CDMO. The CDMO's QMS is needed to support change controls, planned and unplanned deviations, and any investigations that are required. These areas are especially important when it comes to batch release, product development report writing, and/or regulatory filings.

Packaging and Labeling Capabilities

Another area for examination is whether the CDMO has integrated clinical service offerings. Some do and some don't, and the client will have to decide if this is a service offering they'd like to see from their CDMO or if they will rely on a third-party organization that specializes in this activity. If the CDMO will be performing any of these activities, their packaging capabilities that will need to be understood. Most CDMOs can package in HDPE bottles so this may not be an area of concern. However, during the clinical stages, many products are packed in blister packs. There is also a possibility to need product packaged in sachets in the case of granules used for pediatric or geriatric trials. Blister packaging and sachet filling products are two additional offerings of a CDMO that could be valuable to the program. A CDMOs ability to work with label providers as well as ultimately shipping to clinical sites could be advantageous. In addition to the site's capabilities for packaging and labeling, their readiness for serialization and eventually aggregation to satisfy the requirements of the Drug Supply Chain Security Act (DSCSA) will need to be examined, especially for a later-stage project that may be close to commercialization.

Conclusion

These are high-level items to be considered when choosing the right CDMO for a project. Each project is unique and will come with nuances that will necessitate focusing on certain areas more than others. The important thing to keep in mind is that every project is multi-faceted and careful consideration must be given to numerous areas to make sure the final decision is made only after a thorough examination of all the areas that will likely affect the overall success of the project.

ABOUT

Syner-G

Since 2007, Boston based Syner-G has become a leader in supporting life science organizations across the development continuum from product design to commercialization. With more than 200 team members world-wide, and deep expertise in product development (CMC), regulatory strategy and submissions, and quality assurance, Syner-G offers a full complement of strategy, execution and program management, and submission support services. Syner-G integrates information and messaging around quality, safety, efficacy and competitive positioning, crafting the story behind the science. Syner-G offers comprehensive consultative outsourcing that supports the efficient movement of innovative discoveries through the pipeline to where they can make life enhancing and life-saving impact.

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