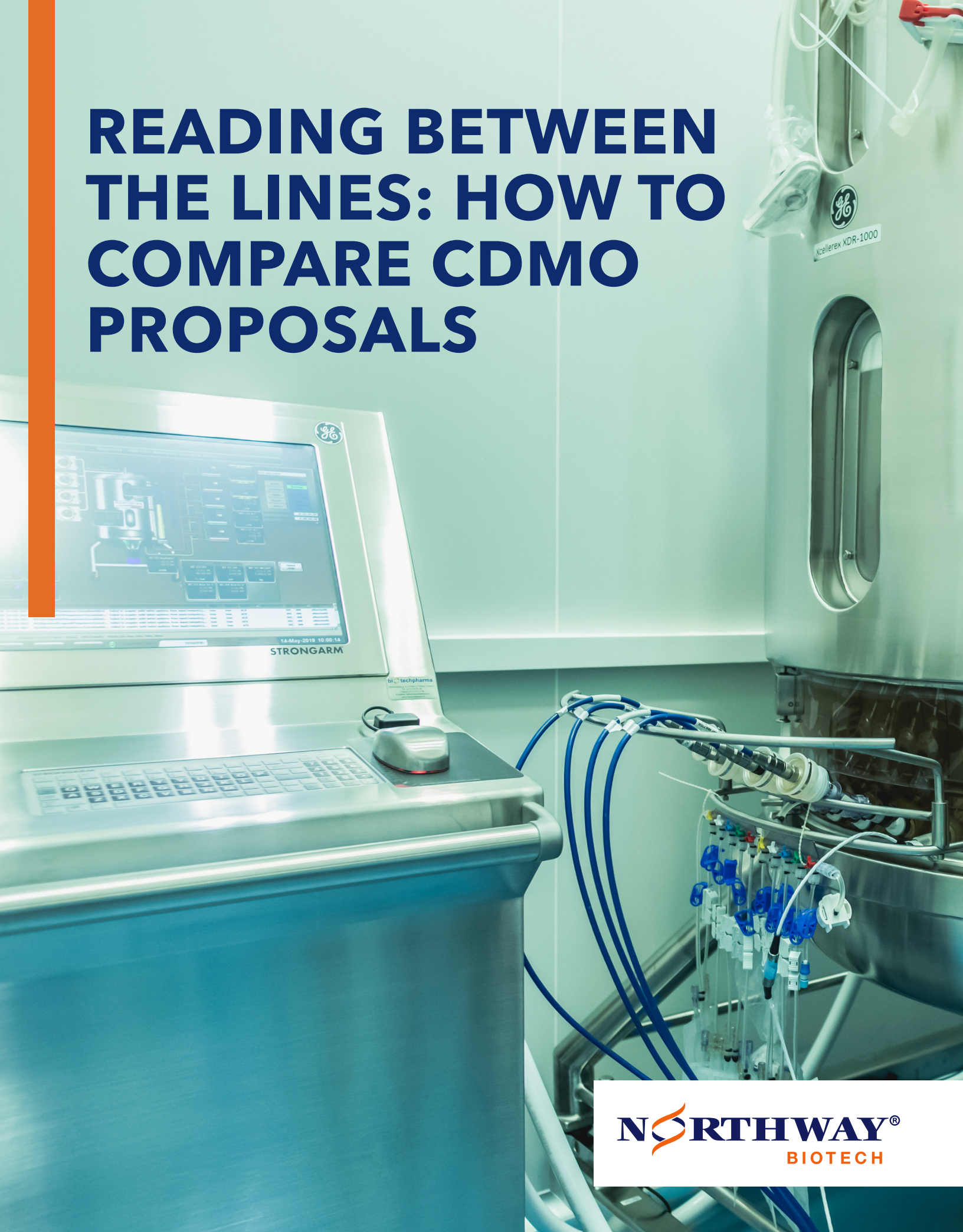
READING BETWEEN THE LINES: HOW TO COMPARE CDMO PROPOSALS



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READING BETWEEN THE LINES: HOW TO COMPARE CDMO PROPOSALS

By Vladas Algirdas Bumelis, Prof., Patrick Haddad, Ph.D., and Rose Rhomberg, Northway Biotech

CDMO proposals often vary in level of detail and depth of explanation, preventing a lateral comparison. However, CDMO clients can take steps to ensure more uniformity between competing offers.

When biotech and biopharma firms seek a CDMO for drug development and/or manufacturing, price is the second most important consideration behind the combination of technical fit, capabilities that match the project, and track record.[1] However, getting a complete answer on CDMO pricing and what exactly the stated figures cover – allowing for true apples-to-apples comparisons between vendors – is difficult. No standard guides how biotech/biopharma firms should prepare their requests for proposal (RFPs), nor does a standard guide how CDMO proposals are prepared and presented.

Nonetheless, understanding best practices in preparing an RFP well-suited to your project's current stage is a strong first step toward a prosperous, transparent partnership with your CDMO. Additionally, knowledge of what to expect from a CDMO's proposal as well as the questions to ask when some aspect of the service appears to be missing or unusually priced, helps establish clear communication and expectations from the project outset.

WHY ARE PROPOSALS OFTEN SO DISPARATE?

A driving force behind the information included in a proposal is the CDMO's management and business practices. One business philosophy might dictate providing generic pricing up front and handling any additional costs through change orders, while another approach might involve comprehensive pricing up front, so the client doesn't receive unexpected surprises on the bottom line.

Some CDMOs have templatized proposals, not scrutinizing the context of a client's particular challenges, usually resulting in a lower initial price compared to a more comprehensive proposal. With a more detailed proposal, the initial estimate may be higher, but the proposal is both more informative and transparent. In the latter scenario, the client benefits from greater transparency because often they are investor funded, thus responsible to a board, a budget, and forecasting projections. So, a CDMO estimate that increases by 20% or 30% because of misinterpreted line items or changes made after the fact can significantly increase the project cost.

Other times, proposals provide only part of the overall project cost because of a CDMO's limited capability. For example, a CDMO client needs to factor in costs for a tech transfer between the drug substance (DS) and drug product (DP) CDMOs when fully integrated services are not offered. Thus, the DS proposal received is not technically incomplete (per that CDMO's responsibilities to the client); it just doesn't include the full scope of

work necessary to complete the project. In addition, a previous CDMO working with the DS may claim some of the changes they've made are proprietary, so they want to charge the client fees that need to be factored on top of the tech transfer costs from the incoming CDMO.

Often, though, lack of detail in a proposal is a result of the client's RFP. Proposals run the gamut from extremely detailed – including quantities, expected timelines, cGMP requirements, how many engineering batches will be produced, etc. – to spartan, lacking in significant details. Generally, the more precise and detailed the RFP, the more realistic and accurate the proposal. Still, the CDMO's business development (BD) team, with whom the client works, can play a significant role in ensuring all possible detail is captured – whether or not it is in the RFP – by guiding and collaborating with the client throughout these early interactions.

DETAILED RFPS = DETAILED PROPOSALS

It warrants mention that vague RFPs are not always mistakes. Some are just the result of a product in an early development stage, submitted so the client can gather more data in support of investment. Sometimes, the client can only provide an informal budget because they are unable to be precise about their exact needs (e.g., quantity requirement). Still, the resulting proposal will be built on assumptions, and the price could double by the time the full project is known.

Early-stage and late-stage clients face different challenges in assembling a comprehensive RFP, as well. For example, early-stage clients may have only a few employees and limited funding. While it is generally advisable for such a client to hire a CMC consultant – they know the questions to ask the biotech to glean correct information for the RFP – such experts can be expensive to retain. Conversely, late-stage customers need to factor in process characterization and process validation for both DS and DP. Exact RFP requirements are dictated by the process and who is involved. Again, retaining a CMC consultant is key, but it also is important to secure a CDMO partner dedicated to educating clients throughout the process from early- to late-stage.

To this end, a proposal should define foreseeable risks, educating clients on the implications of using a given strategy. For example, if the CDMO uses mini pools for process development, then even though the mini pool is representative of the final clone, it may not be exact. So, when the final clone is selected, it may not produce the exact same titer or some of the development may need to be redone. It is vital that clients read through the list of risks and discuss them with the CDMO, weighing the pros and cons of each strategy (i.e., one process might be less expensive but is more likely to produce a failed batch, versus a more expensive process with higher reliability).

Additionally, proposals should detail whether the CDMO offers the use of company-owned, shared, or dedicated columns. For example, if a CDMO were to use a company-owned column, wetted parts would have to be changed, costing between $5,000 and $15,000. Conversely, use of a dedicated column in this scenario could cost between $140,000 and $180,000 – a significant hidden cost to discover after an MSA has been signed.

THE DELIVERABLES ARE IN THE DETAILS

When CDMO leadership collaborates heavily with BD to gain a clear picture of clients' philosophies and expectations, it helps to guide the information in proposals. Still, CDMOs depend on the RFP to lay the groundwork for any proposal. As stated above, these generally arrive in two forms: very detailed RFPs, usually prepared by a senior consultant or the CMC manager, and sparse RFPs, usually prepared by a client that needs a proposal for purposes of budget preparation.

Detailed RFPs ensure a CDMO understands all the requirements. They usually are reviewed by both the BD team and a technical committee (TC), followed by one or more technical meetings with the client, before the CDMO submits an equally detailed proposal outlining included/omitted activities.

Indicative proposals, based on sparse RFPs, generally include few details, just timelines and cost tables relevant to activities proposed to complete the project. The indicative proposal may have a latitude of about 25% to 30% since many project specific details are still unknown, but it is useful to provide a range for early investor meetings. However, the estimate is likely to rise as the depth of necessary services emerges. Similarly, proposals based on project trans-

fers from one CDMO to another contain a margin of error. In addition to technical/equipment disparities, different CDMOs operate with different expectations and pricing strategies.

For example, a CDMO does not see batch production records until after the proposal is signed. A client may state they are transferring a process and all the development work is complete; they just need to scale up their process and begin cGMP manufacturing. However, it is not uncommon for a CDMO to open the document package and realize a client has used a non-scalable process (e.g., one that uses non-cGMP materials) or is missing key assays. In such scenarios, the proposal must be amended to include additional development activities.

Ultimately, proposal content falls into one of three buckets. The first bucket comprises services provided. The second bucket encompasses materials included in the proposal versus those that will incur additional cost, and the third bucket covers outsourced activities.

1. **Services –** A proposal's services bucket should include a list of deliverables for each stage. For example, it might state the CDMO conducts upstream development at small scale (2-5 L), followed by two confirmation runs at 5-10 L before proceeding to downstream development. Such detail in the deliverables is key if a client is trying to compare one proposal to another. If a competing proposal does not include the number of confirmation runs, or it stipulates engineering runs at a different scale, that automatically changes the price, precluding an apples-to-apples comparison.

   As another example, will the client own, or have ready access to, documents the CDMO produces? Seek a proposal where each stage includes a description explaining exactly what activities are performed, enhanced with a deliverables list.

2. **Materials –** Understanding which materials are included in the price versus which will be billed separately is another aspect of comparing CDMO proposals. Proposals that include the raw materials increase the initial bottom line but trim the cost of materials added via a change order later.

   Additionally, the proposal should be up front about which brands are producing the materials. For example, for resins, one vendor might quote Brand A while another quotes Brand B. If each proposal simply states "protein A resin," and one costs $1 million while the other costs $250,000, the client may be unaware whether brand is the reason. This matters because Brand A is very well established – reducing client risk by utilizing a supplier with a proven track record – whereas Brand B is a newer resin. Although Brand B has a good track record, it is just not used as commonly, and the client must have that context to make an informed decision.

   Finally, clients should inquire about material lead times. In the era of COVID-19, numerous global supply chains have been impacted. A client may want to use the more premium resin, but its lead time (for the volume the project requires) could be over a year. So, they might consider alternative materials to avoid delays.

3. **Outsourcing Costs –** CDMO clients should understand clearly which activities will be conducted in-house and which will be outsourced, because those costs are passed on to the client, plus a pass-through cost. For example, virus clearance studies traditionally are outsourced because the contamination risk for many CDMOs precedes conducting that work in-house. If you do not see such a study listed in the proposal, ask about it – that single activity can incur a $100K+ outsourcing cost. Also, some proposals include an outsourced activity line item simply labeled "pass-through," but its cost is not factored into the estimate. If, for example, a CDMO needs to outsource half of a project's assays, including them in the proposal as "pass-through," down-the-road costs may be significant.

DOES THE PROPOSAL STATE A MINIMUM REQUIREMENT FOR PROJECT KICKOFF?

The information and fee required to begin a project depend on where the project starts. For example, if it starts with the DNA sequence and progresses through the entire process – upstream, downstream, analytics, formulation – all the way through cGMP manufacturing of both the DS and DP – an end-to-end CDMO partner should have a strong understanding of the pricing because it will implement its

own process for all those steps. Accordingly, end-to-end CDMO proposals do not include extra costs for concert between DS and DP manufacturing because both are managed internally, which also reduces project timelines.

At Northway Biotech, the first steps in a collaboration are project design and material procurement, with a limited cost to be paid up front. Other CDMOs charge varying amounts to reserve a slot and begin the project, some determined by a percentage of the overall cost estimate. This can be problematic if a client has to produce, say, 30% of a $5M project, tying up a lot of capital for an extended period of time (i.e., there may be a wait of several months before their cGMP slot is available).

We also can be adaptable from a terms and conditions standpoint, quickly beginning projects even before the MSA (which must be in place by the time the cGMP batch is ready to start) is negotiated. Further, regarding the use of cell lines, Northway Biotech can use a research license to perform work until commercialization. Competing CDMOs generally require clients to negotiate directly with the cell line provider or have a proprietary cell line that may not be transferrable. Reducing the number of organizations with which clients must maintain agreements simplifies their process and helps to reduce their cost burden.

CONCLUSIONS

Ultimately, it is critical to select a CDMO that is a collaborative partner versus a transactional partner that is happy to provide a generic proposal template. Establishing a personal relationship with a CDMO and poring over project details up front, through in-depth, formative conversations, establishes a base of trust and comfort between partners. More important, it allows for education between them.

Educating the client is the linchpin of helping them weigh cost versus quality as they compare proposals that may differ greatly on content and clarity. An experienced CMC consultant can help biotech/biopharma companies articulate a robust RFP, and having a CDMO partner identify how its proposal differs from others, so you can make a lateral comparison, is invaluable. In the end, the onus is on the client to follow up on any proposal that might be unclear or omits important information, but one must realize something is muddled or omitted to ask about it.

Another point of comparison is the access a CDMO offers its clients and potential customers. Discover whether a CDMO's clients have access to cameras that allow them to see the project, including visibility into areas that might not have windows. Ask about their policies on virtual meetings. Also, inquire about their person-in-plant (PIP) policies. Since each project is someone's baby, they often want to be involved in each step of the CDMO's work. More collaborative CDMOs embrace these opportunities to discuss a project's direction as well as suggest alternatives or improvements that can help advance a stalled project. However, it is up to the CDMO to strike the right balance between accessibility and speed, as a client deeply involved in every action can lead to delays.

Through all these considerations, keep in mind a proposal is not usually a comprehensive document. It is a baseline, the foundation on which a CDMO and its client establish a process and build the discussions that will grow into a partnership. With so many surprises and disparities possible between proposals, biotech and biopharma organizations should seek out partners who are transparent about every line item, are enthusiastic to educate clients (about costs, timelines, and what is possible), and boast the organizational resources and flexibility to deliver on their commitments.

REFERENCES

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ABOUT THE AUTHORS

Vladas Algirdas Bumelis, Prof., is the Founder and CEO of Northway Biotech. He holds PhDs in both chemistry and biotechnology from Vilnius University and is a full member of the Lithuanian Academy of Sciences. Prof. V. Bumelis has extensive experience in the pharmaceutical and biotech industries, having previously served in senior management positions at international companies in the biopharma industry such as Teva Pharmaceuticals, Sicor Inc., Biofa, and Biotechna. His illustrious career has been recognized many times. In 2004, Prof. V. Bumelis received the Science Award of Lithuania in recognition of his achievements in the development and production of recombinant proteins, while in 2012, he was named CEO of the year in Lithuania. Vladas can be contacted at vladas.bumelis@northwaybiotech.com.

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ABOUT NORTHWAY BIOTECH

Northway Biotech is a leading CDMO supporting customers worldwide. Its highly experienced, professional team executes projects at any stage, from cell line construction and process development to cGMP manufacturing of biopharmaceutical products. The company's wide-ranging expertise and vertically integrated service offering translate to the ability to rapidly execute multiple projects from its state-of-the-art GMP facilities while ensuring full process and product compliance at all stages of research, development, and commercial manufacturing. Northway Biotech is a privately owned company founded in 2004 and located in Vilnius (Lithuania) and Waltham, MA (USA).

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