INTEGRATED DRUG MANUFACTURING

A SERVICE OFFERINGS PRIMER

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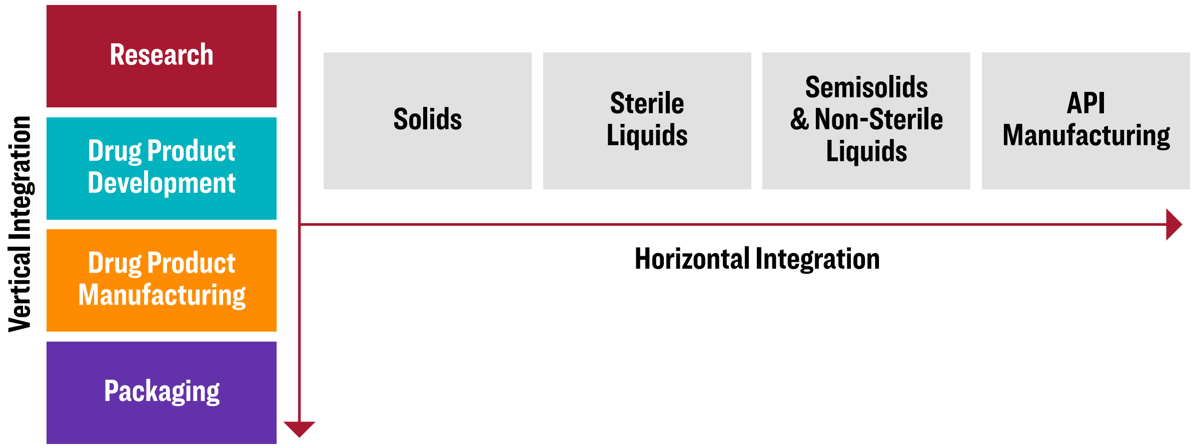
The Health Science EXPERTS

CONTENTS

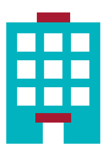
INTRODUCTION/TERMINOLOGY

Horizontal and vertical integration are two main types of integration for businesses. Horizontal integration is where one company takes over another that operates on the same level within an industry. Vertical integration occurs when one business takes control of one or more stages of production to gain more control of the overall process.[1]



Source: Shuchi Nahar's Blog, "A Masterclass on Global Custom Development & Manufacturing Opportunity" (7/12/20)[2]

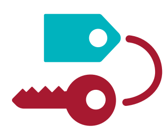
Within the CDMO/CMO industry there are multiple terms with overlapping definitions. Though distinct, they are often used interchangeably with integration.



One-Stop Shop: a firm that offers a multitude of products or services to its customers, all under one roof[3]

End-to-End: a principle that takes a system or service — from beginning to end — and delivers a complete functional solution usually provided by a single source[5]

Full-Service: a CDMO that can provide support through all stages of drug development and formulation for all types of drug substances and project timelines[4]



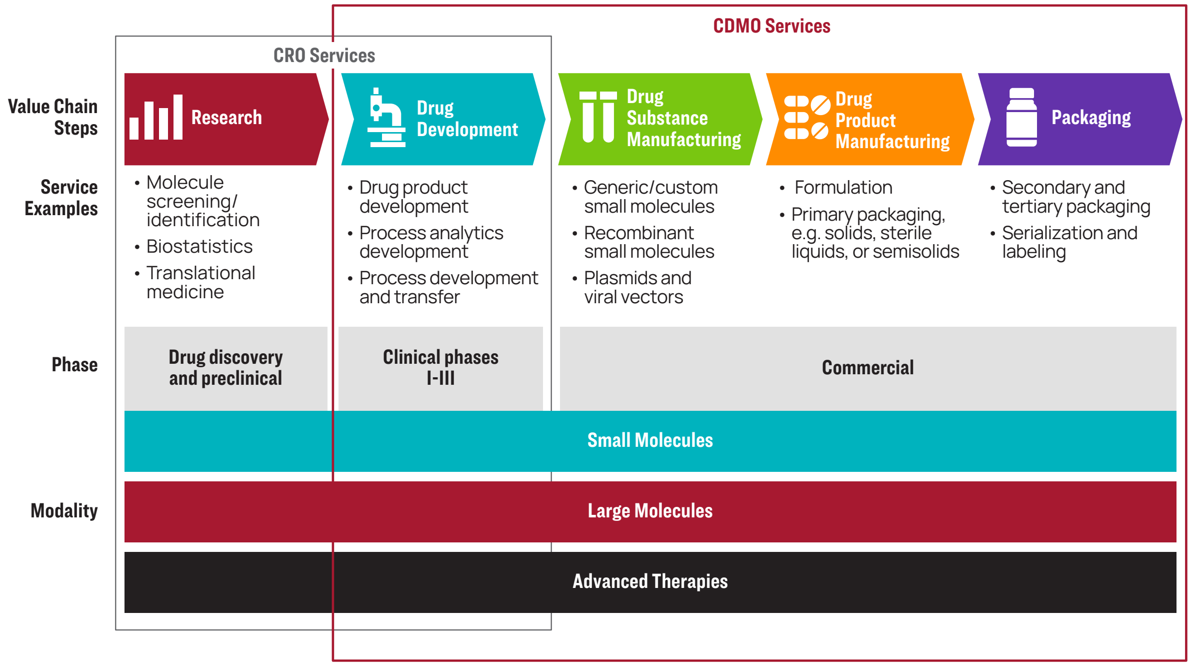
Turnkey: a simplified process where clients need not worry about coordination or compatibility between multiple companies[6]

BROADER/MORE COMPLEX OFFERINGS

The CDMO industry itself is relatively new. Prior to 1996, there were few dedicated contract drug manufacturers. But starting in 1996, a combination of three factors: the shedding of excess manufacturing capacity by global biopharma companies, a dramatic increase in early-stage biopharma companies, and the success of contract research organizations furthered the growth of the CDMO industry.[7]

Pharmaceutical industry growth has also fueled growth in the CDMO industry. The number of pipeline products and the proportion of large-molecule products has more than tripled since 2001.[8] And as the size of the pipeline has increased, drugs themselves have become more varied, drug manufacture has become more complex, and the CDMO value chain has broadened.[9]

Overview of CDMO Services



Source: PWC-Strategy&, "2022 Global CDMO Study of Pharmaceutical Operations" (May 2022)[10]

As seen in the above graphic, the value chain has broadened horizontally (represented by the modalities) and vertically (represented by the extension of stages from drug development to manufacturing to packaging). Drug products have continued to become more varied with the advent and growth of advanced therapies. Additionally, with drug substances becoming more complex, there is an increasing need for faster innovation.[11]

THE RISE OF THE ONE-STOP SHOP

The current CDMO sector is characterized by a few dominant players; the top CDMOs have just below one-fourth of the market with 500+ smaller, niche CDMOs.[12] Consolidation is continuing to steadily grow.[13] The market will continue to consolidate as CDMOs continue to acquire necessary scale and capabilities that sponsors demand, with the one-stop model being a way CDMOs can differentiate themselves.[14]

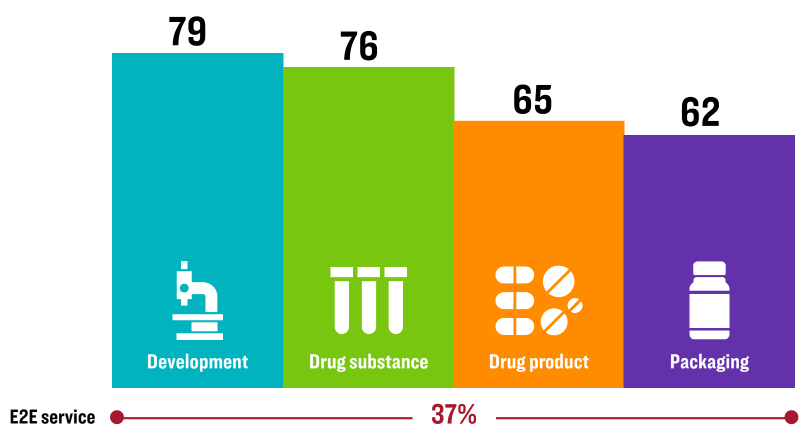
"The CDMO value chain is moving toward a 'one-stop shop' service portfolio. ... Customers increasingly expect CDMOs to provide expertise along and beyond the entire manufacturing process, including commercial launch."
(EY-Parthenon Analysis)[15]

A one-stop shop model is especially becoming the strategy of choice for larger CDMOs. Smaller CDMOs are more likely to provide end-to-end services for small to midsize biotech or specialty pharma companies.[16]

Most (if not all) of the largest CDMOs — including Catalent, Lonza, and Patheon — function as one-stop shops. They provide end-to-end services across multiple modalities (e.g., small molecule, large molecule, advanced therapies). And a growing number of small to midsize CDMOs provide end-to-end services for at least one type of product (e.g., oral solid dose manufacturing). However, how CDMOs position themselves does not always align with these definitions.

According to a 2022 PWC analysis of more than 150 CDMOs (see chart below), for each of four service categories — development, drug substance manufacturing, drug product manufacturing, and packaging — the proportion of CDMOs that offer these services ranges from 62 to 79%. Thirty-seven percent of CDMOs offer end-to-end (E2E) services (i.e., services in each of the four categories).

Services Offered by CDMOs Studied



Source: PWC-Strategy&, "2022 Global CDMO Study of Pharmaceutical Operations" (May 2022)[17]

The consolidation of CROs in the contract research organization space might be a precursor to how consolidation will play out in the CDMO market:

- The CRO market, like the CDMO market, had been highly fragmented; by 2019, however, the top five CROs accounted for about 70% of total market share[18]
- In the past decade, many large biopharma companies moved from working with a set of preferred providers to forming strategic partnerships with one or two CROs; these CROs expanded their offerings to improve their chances of winning the strategic partnerships[19]

BENEFITS OF THE ONE-STOP SHOP MODEL

There are numerous potential benefits to a CDMO offering a one-stop shop model. Benefits are either general in nature or quite specific. General benefits can be for either or both the CDMO and sponsors.[20]

Benefits to CDMOs include:

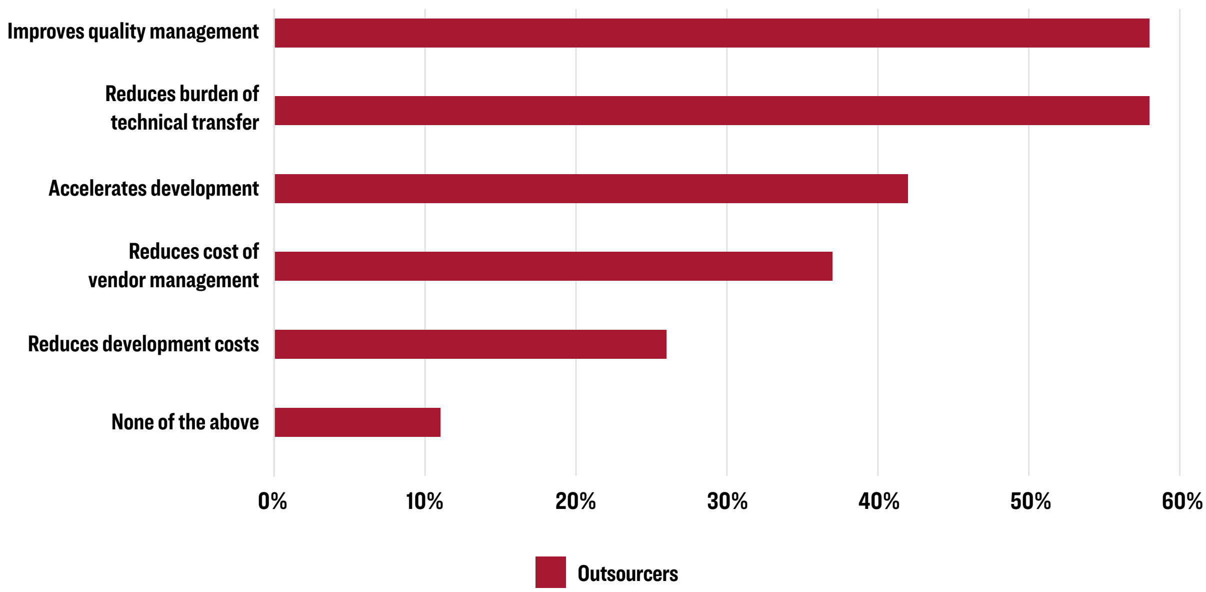
- An opportunity to diversify revenue streams
- Potential to capture a larger market share
- Enhancing its status as a strategic partner

Benefits to the sponsors include:

- Single provider
- Shorter timelines due to enhanced accountability
- Harmonization of systems

Specific benefits are presented in a 2019 Pharmaceutical Outsourcing-SCORR survey of sponsors. According to this survey (see chart below), more than one-half of outsourcers believed the one-stop shop model results in improved quality management and reduced burden of technical transfer.

Benefits of One-Stop Shop Model

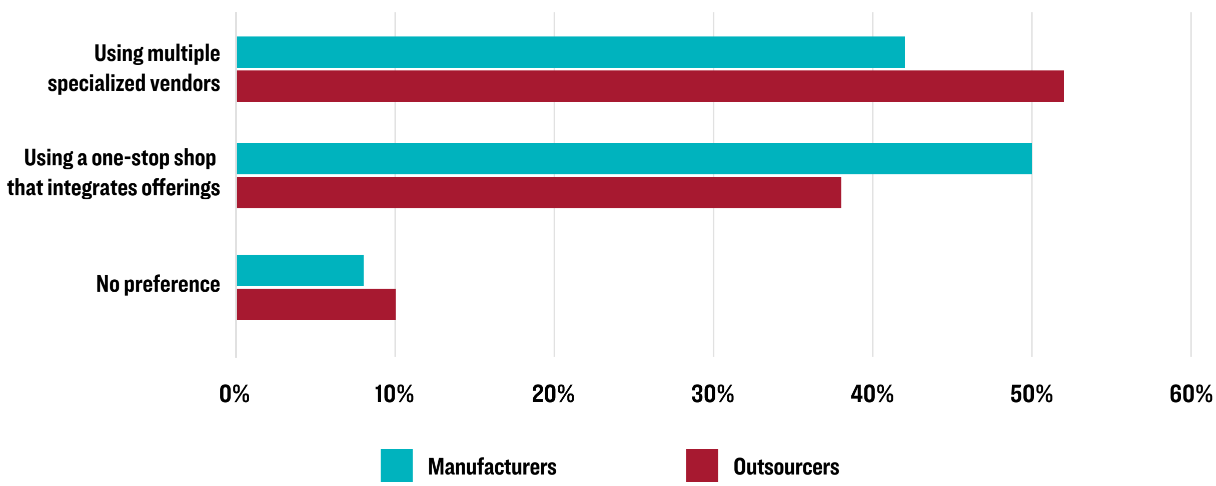


Source: Pharmaceutical Outsourcing-SCORR, "Evaluating the Outsourcing Dichotomy" (May 2019)[21]

DISADVANTAGES OF ONE-STOP SHOP MODEL

While CDMOs are increasingly branding themselves as one-stop shops, not every sponsor is looking for that. According to the same 2019 Pharmaceutical Outsourcing-SCORR survey (see chart below), more than one-half of outsourcers prefer using multiple specialized vendors (though drug manufacturers themselves prefer using a one-stop shop to integrate offerings).

Preferences for One-Stop Shop Model



Source: Pharmaceutical Outsourcing-SCORR, "Evaluating the Outsourcing Dichotomy" (May 2019)[22]

More specific downsides to incorporating a one-stop shop model exist for both CDMOs and sponsors.[23]

Disadvantages from the perspective of a drug manufacturer include:

- Increased organizational complexity
- Need for diverse sets of skills
- Risk of appearing as a "jack of all trades, master of none" to customers

Disadvantages from the perspective of the sponsors include:

- Increasing dependence on the supplier
- Loss of bargaining power
- Times when the CDMO is not the best at certain stages
- Greater difficulty in switching to a different CDMO

Some sponsors could be looking for an alternative to the one-stop shop model. For example, smaller or midsize sponsors might be looking for CDMOs that are the "right size" for them rather than a "one-stop shop."[24,25] And being a right size and one-stop shop CDMO is sometimes incompatible.[26]

M&A DECISION CALCULUS

As seen in the EY Parthenon graphic below, there are distinct types of and reasons for mergers and acquisitions. A CDMO's size affects the type of M&A choices available to it. For example, a very large CDMO is better able to consider M&A activity that results in both horizontal and vertical integration, while a large CDMO is more likely to have to choose one or the other.

	Players at scale	Extenders	Complementors
Company archetype	Very large companies/conglomerates (>US$5B annual revenue), with wide range of products and services	Large companies (US$0.5B-US$5B in yearly revenue) with existing CDMO services and broad offering	Smaller scale CDMOs with more limited product and services offering focused on few modalities/value chain elements
CDMO M&A activity	Conducting multiple deals to leverage economies of scale by broadening their range of services	Purchasing selected assets to add capabilities in a strategic way	Acquisition of companies active in adjacent spaces connected to the buyer's core business
Growth trajectories	Universal expansion: horizontal + vertical	Directed expansion: horizontal or vertical	Surgical investment
	Modalities	Modalities	Modalities
	Value chain/technologies	Value chain/technologies	Value chain/technologies
	Product/service combinations	Product/service combinations	Product/service combinations
	Customer types (early/late stage)	Customer types (early/late stage)	Customer types (early/late stage)
	Geographies	Geographies	Geographies

Source: EY Parthenon, "How CDMOs are leading innovation for pharmaceutical partners" (7/14/22)[27]

CDMOs — especially the larger ones — are often looking for smaller CDMOs that can extend or complement their existing portfolio of service offerings. They use M&A to fill a void in capabilities.[28] Because companies can more easily acquire other companies than develop services from internal investment, it is difficult to find end-to-end CDMOs that function as a single provider that did not acquire companies.[29]

Examples from 2022 of CDMO M&A activity are:

- MilliporeSigma Acquires Erbi Biosystems (Dec. 2022)[30]
- Catalent to purchase Metrics Contract Services from Mayne Pharma (Aug. 2022)[31]
- Cambrex Acquires Q1 Scientific (June 2022)[32]

CRDMOS/CTDMOS

Results Healthcare notes the emergence of an end-to-end model that integrates CRO and CDMO functions: CRDMO (see graphic below): Contract Research Development and Manufacturing Organization. These are functions that previously have operated as separate entities (i.e., NOT a one-stop shop).

CRO	CRDMO	CDMO
Drug discovery and drug development services, including: › Biopharmaceutical development › Biologic assay development › Commercialization › Preclinical research › Clinical research › Clinical trials management › Pharmacovigilance	Bridging services: › Pre-formulation, formulation development › DMPK studies › Safety studies › Biological analysis › Preclinical & Phase I clinical trial materials › Stability testing and scale-up	Manufacturing and development services, including: › Commercial production › Formulation services › Stability studies › Method development › Late-stage clinical trial stage materials › Formal stability › Scale-up › Registration batches

Source: Results Healthcare, "CRO sector: M&A drivers and market trends," (February 2022)[33]

Drug discovery and preclinical service outsourcing has increased, due in part to the CRDMO model gaining traction.[34] This trend, observable over the past five to eight years, has seen companies market themselves as one-stop shops and CRDMOs, with larger biopharma companies preferring to partner with multiple contractors while smaller companies prefer to partner with a CRDMO.[35]

Some companies with both CDMO and CRO services still market them independently:

- Charles River Preclinical CRO and Cell and Gene Therapy CDMO
- Quotient Sciences

Others promote "CRDMO" branding on their website (Contract Research Development and Manufacturing Organization):

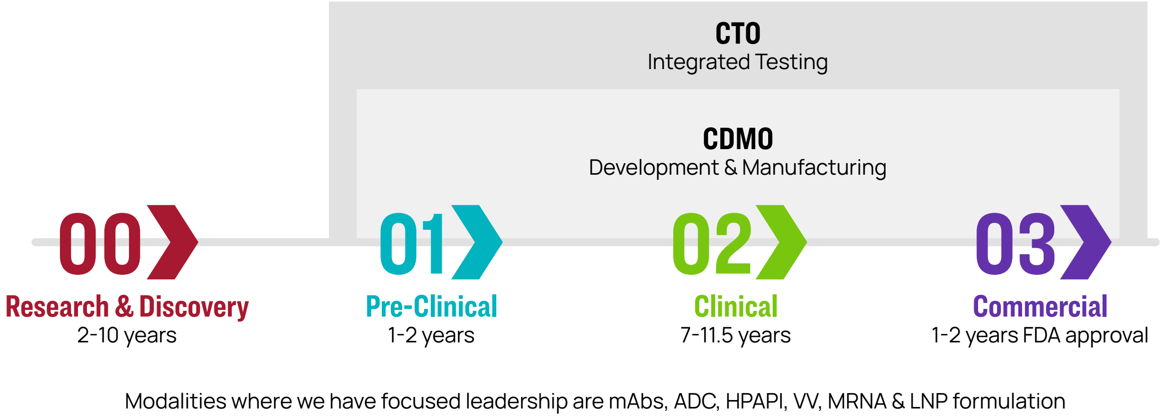
- Bioduro-Sundia
- Curia
- Eurofins
- Jubilant Biosys
- WuXi Biologics

CRDMOs further expand the value chain. They differ from CDMOs in their ability to offer contract research-related services such as preclinical testing or clinical trials management (i.e., the "R" in "CRDMO"). The larger CRDMOs offer a broader range of services and function like supercharged one-stop shops. Smaller to midsize CRDMOs function like supercharged end-to-end companies.

Yet still other companies describe themselves as "CTDMO" (Contract Testing Development and Manufacturing Organization):

- MilliporeSigma
- WuXi Advanced Therapies

As stated above, the CRDMO abbreviation is a melding of the CRO and CDMO abbreviations as CRDMOs offer both contract research and contract development manufacturing services. CTDMOs differ from CRDMOs in that the CTDMO abbreviation comes from the "T" for contract "testing" and the CDMO abbreviation. MilliporeSigma, who coined this term in early 2022,[36] describes CTDMOs as "support [for] clients seeking a single partner who can leverage technical leadership [with] a unified and simplified experience covering the entire value chain."

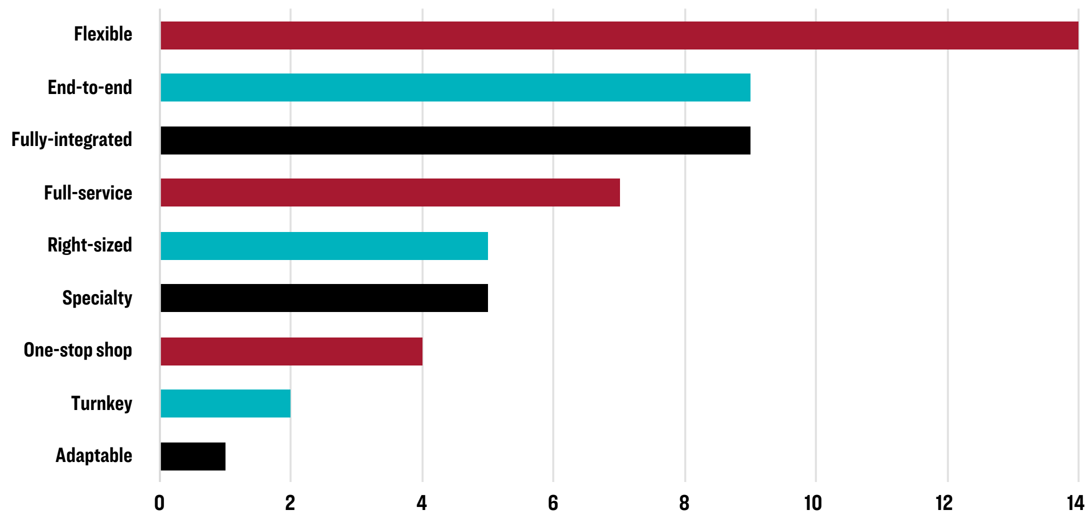


Source: MilliporeSigma website, "Millipore® CTDMO Services"[37]

HOW CDMOS/CMOS POSITION THEMSELVES

In reviewing 47 CDMO websites to see how they describe themselves, the frequency and specificity of usage of certain positioning keywords or phrases are as follows:

Number of CDMOs That Position Themselves With Specific Keywords/Phrases

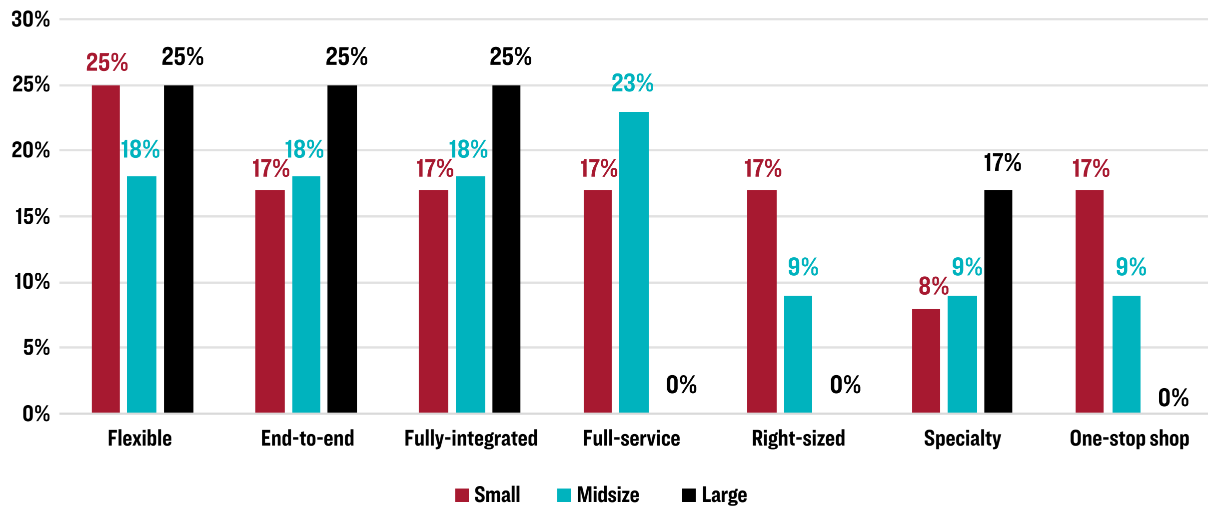


Source: SCORR analysis of 47 CDMO websites from 3/6/23 thru 3/24/23
Note: These are counts of which CDMO sites positioned themselves as one or more of the above keywords on their website's homepage, news/press releases, title tag, or prominent interior pages within one click of the homepage, including but not limited to Services or blog posts

Some observations:

- While more CDMOs (especially large ones) have moved toward a one-stop shop model, few of them prominently position themselves as a "one-stop shop." The review of 47 CDMO websites found only four CDMOs that did so:
  - Adare
  - Biovian
  - Hemoteq
  - Langhua
- Instead, CDMOs are more inclined to promote themselves as "flexible," a provider of "end-to-end" services, "fully-integrated," or "full-service."
- Five smaller to midsize CDMOs opt to present themselves as "right sized":
  - Ascendia
  - Cambrex
  - LLS Health
  - Seqens (PCI Synthesis)
  - Shilpa Biologicals

CDMO Positioning by Size



Source: SCORR analysis of 47 CDMO websites from 3/6/23 thru 3/24/23
Note: These are counts of which CDMO sites positioned themselves as one or more of the above keywords on their website's homepage, news/press releases, title tag, or prominent interior pages within one click of the homepage, including but not limited to Services or blog posts. Company size information comes from the number of employees according to the company's LinkedIn/About page. Small = 500 or fewer. Midsize = 501-5,000. Large = 5,001+.

Some additional observations:

- The most utilized positioning keywords by size are:
  - Small → "Flexible"
  - Midsize → "Full-service"
  - Large → 3-way tie between "Flexible," "End-to-end," and "Fully-integrated"
- "Right-sized" used by only small and midsize CDMOs
- "One-stop shop" also used by only small and midsize CDMOs; while large CDMOs increasingly behave like one-stop shops, they don't promote themselves as one-stop shops

EXAMPLES OF HOW CDMOS/CMOS POSITION THEMSELVES

"Flexible"

"We love to share our unparalleled knowledge, dedication, and flexibility with you as we help you move from promise to production."

"We can be very flexible now with our clients working with any size client at any stage of the product development cycle."
(Robby McGarry, General Councel, Kindeva)[38]

"End-to-end"

"Curia is an end-to-end CDMO built to help pharmaceutical and biotech companies improve patients' lives."

"Fully-integrated"

"Put our unmatched technical expertise and fully-integrated drug development and manufacturing services to work for you."

"Full-service"

"With our full-service offering, we are your partner of choice."

"Right-sized"

"Pharmaceutical companies now require a right-sized partner that shares similar values and vision."

“Specialty”

alcami

“We are equipped and experienced in a broad assortment of specialty capabilities to provide solutions to your drug development process and validation challenges.”

“One-stop shop”

BIOVIAN

“Biovian is a CDMO providing One-Stop-Shop services in GMP manufacturing.”

“Turnkey”

NOBLE PHARMA LLC a Vets Plus Company

“Noble Pharma – A Turnkey Pharmaceutical CDMO.”

SUMMARY

01 **The CDMO value chain has broadened over time, both horizontally and vertically.**

02 **Large CDMOs, especially, have adopted the one-stop shop model.**

Benefits to CDMOs	Benefits to Sponsors
Diversify revenue streams	Single provider
Capture more market share	Shorter timelines
Enhance status as strategic partner	Harmonization of systems

03 **The broadening of services (and the adoption of the one-stop shop model) is often the result of M&A activity.**

04 **Large CDMOs, however, don't usually promote themselves as one-stop shops even when they behave like them. Instead, they are more likely to position themselves as:**

- "flexible"
- "end-to-end" service providers
- "fully-integrated"

05 **In some cases, they describe themselves as a CRDMO or a CTDMO.**

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