Carbogen Amcis got a head start in antibody-drug conjugates with expertise in highly potent small molecules dating back to 2005 at its facility in Bubendorf, Switzerland.

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OUTSOURCING

New day for antibody-drug conjugates

The drug services sector jolts as ADC approvals ramp up and a slew of candidates enter the clinic

RICK MULLIN, C&EN STAFF

You may have heard of the consulting firm Gartner's technology hype cycle—the technology trigger, the peak of inflated expectations, the trough of disillusionment, the slope of enlightenment, and the plateau of productivity.

Consider the antibody-drug conjugate.

ADCs emerged more than 20 years ago with the promise of improving cancer treatment. The basic idea is to chemically link highly potent small-molecule payloads to antibodies that connect with proteins on the surface of tumor cells, creating a kind of guided-missile approach to drug delivery far less toxic than chemotherapy.

It intrigued the world of cancer research, where highly potent compounds and biologics had been making halting progress on their own. Large drug companies rushed in and lined up for their first shots on goal.

AbbVie took a $6 billion shot with Rova-T (rovalpituzumab tesirine), a treatment for advanced small-cell lung cancer, that it got in 2016 with the acquisition of Stemcentrx. Its failure in 2019 was a shock; many in the sector stopped talking about ADCs. Some, perceiving that the promise of ADCs would not be realized, stopped working on them.

But other drug developers kept busy, and the approvals came. The US Food and Drug Administration approved three ADCs in 2019. By the end of last year, 12 in all had been approved, and 145 ADC candidates were active in the clinic, according to Beacon Targeted Therapies, the drug development intelligence arm of the consulting firm Hanson Wade. The most recent to be approved was Tivdak, an ADC from Genmab and Seagen for recurrent or metastatic cervical cancer.

In addition to being an emerging therapeutic class, ADCs are a ripe opportunity for contract development and manufacturing organizations (CDMOs). An ADC is complicated, requiring an antibody, a payload, a linker molecule to join the two, and conjugation to bring all the parts together. CDMOs have been supplying these services for well over a decade. They are now stepping up with a round of new investments to serve drug firms that are bringing forward the next generation of candidates, including site-specific ADCs engineered to set payload molecules at precise locations on antibodies.

Jake Morris, a senior account manager at Beacon, says recent approvals reflect a high level of steady development. "The approved ones were in development during the recent slump," he says. "It's not as if something changed in everyone's strategy."

Approaches to designing ADCs have evolved, Morris says, but the more evolved candidates are still working their way through the R&D system. "It's quite interesting that all the approved drugs for ADCs are non-site-specific, all using the first-generation approach," he says. But the new generation is coming up fast. "In 2020, every ADC that entered the clinic was site specific," he says.

Large drug companies, their confidence restored by recent approvals, are active in developing ADCs, Morris notes, but most players are small biotech firms that lack manufacturing facilities, creating a lot of work for service providers.

"We see a very strong CDMO business for ADCs," says Matthias Bucerius, head of actives and formulation for MilliporeSigma, the CDMO arm of Germany's Merck KGaA.

The company is well positioned for business going forward, Bucerius says. Over the past several years, it has filled out its ADC services with the acquisition of Sigma-Aldrich; added services for linkers and highly potent payloads at Sigma-Aldrich's plant in Madison, Wisconsin; and introduced conjugation services at Sigma-Aldrich's home base in Saint Louis. Merck KGaA has been manufacturing monoclonal antibodies in Martillac, France, for more than 20 years.

MilliporeSigma is currently investing $65 million to expand ADC-related capacity in Madison. The project will add six high-containment laboratories, according to Bucerius. The company recently expanded its conjugation and clinical-scale manufacturing facility in Saint Louis.

The growth in the number of ADC candidates entering the clinic in recent years is driven by innovative research, Bucerius says. He estimates that 30% of the ADC projects his company is working on are novel-format conjugates, a term coined by Beacon for conjugates that use oligomers, immunostimulants, and chelators for radioconjugates as substitutes for antibodies.

MilliporeSigma has been innovating as well. It introduced a research technology service addressing hydrophobicity, or poor aqueous solubility, the cause of more than 20% of terminations during clinical trials, Bucerius says. Overall, the firm currently provides services for more than half the approved ADCs, he says.

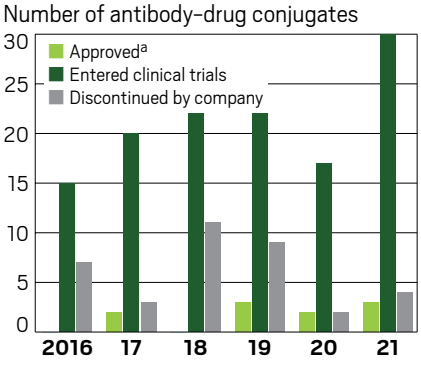
Lonza, one of the world's largest CDMOs, makes monoclonal antibodies and highly potent active pharmaceutical ingredients and provides ADC conjugation services, all at the company's complex in Visp, Switzerland, according to Stefan Egli, head of bioconjugation. Antibodies for ADC work can also be supplied from Lonza's plants in Portsmouth, New Hampshire, and Singapore, where it has larger-scale production.

"There is definitely a moment for excitement in the ADC world," Egli says, pointing to the arrival of new technologies, including ADCs with stabler linkages and improved toxicity profiles.

In response, Lonza is adding capacity for ADC conjugation. This year the company is opening an additional 1,500 m^2 of capacity for conjugation in Visp. Egli says space is also available for ADC customers

ADC dynamics

Antibody-drug conjugates are pouring into the clinic as approvals mount and failures taper off.



Source: Beacon Targeted Therapies.
a All approvals are by the US Food and Drug Administration except for one by China's National Medical Products Administration in 2021.

MilliporeSigma is investing $65 million to expand antibody-drug conjugate capacity in Madison, Wisconsin.

at Lonza's Ibex facility in Visp, a general manufacturing campus at which customers can set up operations.

Piramal Pharma Solutions, an India-based CDMO, put its ADC business together via acquisition. One of its first steps was to launch conjugation services at a facility in Grangemouth, Scotland, that it acquired from Avecia in 2005. Its 2016 purchase of Ash Stevens added payload and linker services. The company performs fill-and-finish work at a plant that it bought from the University of Kentucky in 2015. And last year Piramal acquired a minority stake in Yapan Bio, an Indian producer of monoclonal antibodies.

Stuart Needleman, Piramal's chief commercial officer, says the investment in Yapan is the first step in adding antibody production to the ADC services the company already offers in the US and Scotland.

Meanwhile, Piramal plans to spend $68 million to expand its facility in Grangemouth. The project will begin with the addition of two conjugation suites next year and room to build two more. The firm announced a $32 million expansion of its Riverview, Michigan, site in 2020. Needleman stresses that Piramal has been servicing the ADC market since the early days and provides services to Seagen for Adcetris, the first-approved ADC therapy. "It's a growing space," Needleman says. "But it's down to track record."

Novasep, a French CDMO that recently merged with PharmaZell, also claims a track record. It made its first ADC payload in 2006 at a plant in Le Mans, France, that manufactured small volumes of generic cytotoxic molecules such as docetaxel and paclitaxel, according to Kevin Daley, marketing director for pharmaceuticals. "We just had the perfect fit," he says. "Small-volume cytotoxics and high-performance liquid chromatography, which are absolutely vital for purifying these ADC payloads."

The company produced its first conjugation batch in 2010 and began scaling up its operation, bringing an $11 million bioconjugation unit on line in Le Mans in 2017. The company is providing services for "at least three" commercialized ADCs, Daley says.

It's arguable whether being able to provide a full range of services, including antibody production, presents an advantage over more focused experience with payload and conjugation services, Daley says. Novasep sold its viral vector business, which manufactured antibodies, to Thermo Fisher Scientific last year, and it is emphasizing its strength in highly potent small molecules and conjugation.

"The CDMO business is all about relationships with customers and confidence in technical teams and management," Daley says. "From Novasep's perspective, having the payload and conjugation on one site presents advantages for our customers."

The company is expanding capacity in Le Mans with a $6 million project to add a manufacturing suite for highly potent active pharmaceutical ingredients. The company invested $4 million at the site in 2021. "Our next step forward will be to carry out quality-control analysis," Daley says.

Carbogen Amcis got a head start in ADCs with expertise in highly potent small molecules that dates back to 2005 at its facility in Bubendorf, Switzerland, says Scott Miller, senior scientific adviser at the company. "Early on we were asked to produce a drug linker for an early ADC," Miller says. The company added conjugation services as demand grew.

"The conjugation side really kicked off in 2013 and 2014," Miller says. Carbogen invested in a clean-room lab in Bubendorf and in formulation and fill-and-finish services at its plant in Riom, France. The firm is currently expanding drug linker capacity in Bubendorf and plans to open a new fill-and-finish site in Riom next year.

"Our conjugation services are presently 100% with biotech companies, and most of our proposal requests come from this sector of the industry," Miller says. On the other hand, he says, 75% of Carbogen's business in linkers for highly potent drugs is with larger pharmaceutical companies that do not require conjugation services.

Sterling Pharma Solutions, a UK-based services firm with expertise in highly potent molecules, moved into conjugation in a partnership with ADC Biotechnology, another British CDMO, in 2020. Sterling purchased ADC Biotechnology the following year and recently announced it will spend $1.3 million to expand R&D at ADC Biotechnology's site in Deeside, Wales.

"We saw opportunity in the market," says Colin McKee, head of technical services in Deeside. McKee says that for 8 years, the Deeside plant has been making conjugates in quantities of up to tens of grams to support preclinical research on ADCs. The company is investing an additional $1.3 million for clinical and commercial supply.

"Colin and team have done a great job expanding process development and the clinical development aspect of the site over the last year, close to doubling the number of people on the site, from 30 to 55," says Stewart Mitchell, site head at the Deeside plant.

It is hard to predict whether productivity in ADC development will plateau, in keeping with the Gartner hype cycle. But any disillusionment the sector may have experienced is in the rearview mirror. And service companies are enthusiastic about the challenges ahead—challenges that even the most experienced among them need to be alert to, Lonza's Egli says.

"It always sounds like the chemical part is easy, but this is supercomplex to synthesize," Egli says. And bioconjugation requires experience in the handling of radioisotopes, biopolymers, and oligonucleotides.

MilliporeSigma's Bucerius says the action in the ADC market is encouraging. "I really like that we are talking about ADCs again," he says. "For the past 24 months, all the focus has been on other technologies," he says, primarily messenger RNA–based vaccines. "Therefore, it is great that we are bringing technologies like ADCs to the forefront again, because there is so much going on in that space." ■

> "The approved ones were in development during the recent slump. It's not as if something changed in everyone's strategy."
>
> **—Jake Morris,** senior account manager, Beacon Targeted Therapies

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Chemists can use and make toxic chemicals for many legitimate applications. The Organisation for the Prohibition of Chemical Weapons inspects the facilities where such chemicals are made.

CREDIT: OPCW

CHEMICAL WEAPONS

Confronting AI's toxic potential

Algorithms for drug design can be tweaked to design potential chemical weapons

LAURA HOWES, C&EN STAFF

All it took was a minor edit to Collaborations Pharmaceuticals' code. Suddenly, an algorithm for designing drugs to treat Alzheimer's disease was suggesting thousands of chemical structures for nerve agents instead. Senior scientist Fabio Urbina was shocked. With very little effort, he'd just made a machine for designing new chemical weapons.

Chemical weapons have plagued warfare at least since the ancient Greeks used extracts of hellebore to poison the water supply of besieged cities. But since 1997, the Chemical Weapons Convention (CWC) has banned the development, production, stockpiling, and use of any chemical weapon by convention members, which include all but four countries around the globe. According to the CWC, chemical weapons are toxic chemicals or precursors intended for misuse; munitions and devices to deliver those chemicals; and equipment designed to use those munitions.

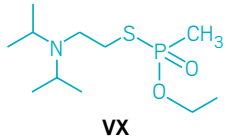
After parties to the convention agreed to destroy their chemical weapons, global stockpiles of the weapons decreased significantly and continue to do so. Despite this, bad actors and terrorist organizations still make and use chemical weapons. That means that organizations that are committed to nonproliferation need to monitor new developments in chemical and biological science and their potential implications.

As part of Spiez Laboratory's mission to protect against nuclear, biological, and chemical threats, it organizes "convergence" conferences every 2 years to identify emerging threats to the international control of biological and chemical weapons. In preparation for a conference held last year, Cédric Invernizzi, who studies nuclear, biological, and chemical weapons control at Spiez Laboratory, contacted Collaborations Pharmaceuticals. He asked the biotech company to consider how scientists could use artificial intelligence drug-design tools, which are intended to benefit human health, for harm instead. "We invited them to present their cutting-edge work," Invernizzi says, "but also to ask them to reflect on the potential for misuse in order to discuss the potential implications, in particular for the chemical and biological weapons conventions."

The ease with which Collaborations Pharmaceuticals generated potential new toxic compounds raised big questions among conference goers and beyond. But while experts debate how significant the threat of AI-designed chemical weapons is, they already agree that questions around dual use—the use of something for both beneficial and harmful purposes—in chemistry need broader consideration.

Creating a credible threat

One of the chemicals listed under the strictest CWC controls is VX, a highly toxic organophosphorus nerve agent developed in the 1950s. VX is one of



VX

Artificial intelligence algorithms could be repurposed to suggest potential chemical weapons.

many nerve agents that block the enzyme acetylcholinesterase, thereby causing muscle paralysis and, without treatment, death. But acetylcholinesterase is also a target of therapeutic drugs. So Collaborations Pharmaceuticals' Urbina and company CEO Sean Ekins realized it would take only a small change to repurpose the company's drug-designing algorithm to favor chemicals with high toxicity scores instead of low ones.

"Oftentimes, with these generative models, we include these toxicity data sets in order to drive the molecules away from toxicity," Urbina says. "So in a sense, we had already had the entire thing set up to go." After changing the code to select for toxicity, Urbina let the algorithm run. He came back the next day to find his program had suggested thousands of compounds with predicted toxicities at the same level as or worse than the toxicity of VX.

Without sharing the structures of potential new chemical weapons, Urbina and Ekins presented their findings at the Spiez Convergence conference last year. Those present recall a ripple of shock going around the room. Filippa Lentzos, who studies science and international security at King's College London, was alarmed. Plenty of chemical weapons may be out there already, she says, but "we don't need more ways to kill people."

On the other hand, Marc-Michael Blum, an expert in chemical weapons detection who chaired the session, believes that while the field should monitor these developments, bad actors probably won't use AI drug-design tools this way immediately. "I see the misuse potential," he says, "but going from there to new chemical weapons is not so trivial."

Chemists would need to do a lot of work to develop the predicted compounds into something stable with suitable characteristics for chemical weapons–filled munitions, for instance, he says. Many existing chemical weapons already exist. Syrian government forces used chemicals like sarin or chlorine in recent years. So why, Blum says, would bad actors need more?

It may not be new compounds that lawbreakers seek, but stealthy ways to make known chemical weapons. AI tools that plan synthesis routes to make target compounds could be misused for this purpose. For example, AI tools could suggest new ways of making chemical weapons to evade detection of their production. One way to do that would be by suggesting new synthetic pathways that use precursors that aren't on watch lists.

Gram-scale syntheses of a poison designed for assassination are trickier to detect than large-scale chemical weapons plants, however, and that's where AI design might prove to be a bigger problem. Smaller-scale productions can slip under the radar, whether at a government facility or in small terrorist cells. Ultimately, Blum says, if people with access to the right equipment and skills want to make chemicals to kill, they can, with or without AI.

Dual-use discussions

While the AI-based design of chemical weapons might not be an imminent threat, a more critical issue for many researchers is the uncomfortable fact that they hadn't considered the problem before. This realization highlights a gap in discussions on ethics and chemistry, especially at the convergence of multiple disciplines.

Collaborations Pharmaceuticals' Ekins says he had never considered the dual use of his technologies before Invernizzi invited him to present at the Spiez Convergence conference. "Thinking about a bad use of the technology or the dual-use potential of software? We hadn't thought about that, honestly."

Ekins worked with Urbina, Lentzos, and Invernizzi to report Collaborations' initial findings and some practical advice for others who use AI for drug design (*Nat. Mach. Intell.* 2022, DOI: 10.1038/s42256-022-00465-9). In particular, they propose more training so that researchers using AI in chemistry don't overlook their work's ethical implications.

Jeffrey Kovac is an emeritus professor at the University of Tennessee, Knoxville, who has explored various questions relating to ethics in chemistry. He thinks the ethical considerations for AI-based chemical design aren't that different from those posed by standard chemical synthesis. "I don't know that the AI researchers need to ask any different questions than the traditional synthetic chemist," Kovac says. For example, all chemists should consider the environmental or security implications of their work. The problem, he says, is that chemists often fail to consider these factors at all.

"Essentially, every decision a chemist makes has a technical component and an ethical component," Kovac says. "Chemists, however, tend to ignore the ethical component."

There are ethical guidelines for chemists to refer to. One set is the Hague Ethical Guidelines, which were designed to support the Chemical Weapons Convention. These guidelines say that "achievements in the field of chemistry should be used to benefit humankind and protect the environment" and that chemists should always be aware of the multiple uses—including the potential misuses—of chemicals and equipment. The American Chemical Society also supported the development of the Global Chemists' Code of Ethics, which builds on the Hague guidelines. These guidelines are available in multiple languages on the ACS website. ACS publishes C&EN.

Stefano Costanzi is a chemistry professor at American University who uses computational chemistry to understand how chemicals affect living organisms. He also works to counter the proliferation of weapons of mass destruction, especially chemical weapons. He says that these guidelines are a start, but they could be developed further with more concrete, detailed examples.

Many of those contacted for this article told C&EN that they believe strongly that the teaching of ethics cannot be limited to a single course or training session. Chemists need to integrate these questions into the curriculum and general practice.

"Every decision a chemist makes has a technical component and an ethical component."

—Jeffrey Kovac, emeritus professor, University of Tennessee, Knoxville

CREDIT: OPCW

"I made this a consideration all the time in my research," Costanzi says. "Should I do this? Should I study this? Is it dual use? Is it something that I can publish? Is it something that I feel comfortable involving my students in? It's something that's always on my mind because I do study these sorts of issues. And I think that if we manage to expand this type of frame of mind to our colleagues, that is a good thing."

AI is ultimately just a tool that can be used for good or ill. Costanzi says computational tools could be used to help enforce the CWC. For instance, he is building software that both researchers and nonspecialists like border-control agents could use to check a database to see if a given chemical is subject to controls (*Pure Appl. Chem.* 2022, DOI: 10.1515/pac-2021-1107). These resources would automate something that can take time even for experienced chemists and could help control the trade in precursors for chemical or conventional weapons. He also argues that the CWC should focus more on monitoring whole families of chemicals rather than listing specific subsections of those families. The poisoning of Russian opposition politician Alexei Navalny, for example, was a crime. But the specific chemical used was not subject to the strictest controls of the convention, because it had a different structure from those listed as known chemical weapons. Costanzi says that mismatch comes from the difference between the policy and scientific worlds. He'd like to see more venues for cross-disciplinary conversations to help close the gap.

Working in concert

On the same day that Urbina, Lentzos, Invernizzi, and Ekins spoke to C&EN, the team briefed the White House Office of Science and Technology Policy. They also have another article under consideration at a journal, Ekins will present to the Organisation for the Prohibition of Chemical Weapons—the organization that implements the CWC—in June, and the team is submitting abstracts to multiple scientific conferences to try to raise more awareness. Their initial experiment, they say, should act as a teachable moment for the field.

"There's no easy fix to this," Lentzos of King's College London says. "This is a process." For her, that means more consideration at every stage, "from research institutions and publishers and governments and everybody. They have their roles to play. But scientists also have a role to play here. And I think scientists have an obligation to educate themselves."

Urbina thinks one way researchers working on AI in chemistry or biology could help is by adding ethical discussions to their research papers. "It would be wonderful if every time I read a paper in this sort of field, I could expect to see some sort of section or some couple of sentences on how it can be misused," he says. "I think it would hopefully be almost an infection of the cultural thought. As you see this in somebody else's paper, you start wanting to put it in your own papers."

Meanwhile, as CEO of Collaborations Pharmaceuticals, Ekins is already thinking about how he might manage access to the company's software to prevent bad actors from building on its experiments. "As an industry, we have to be more vigilant," he says. "This is a growing ecosystem. . . . all of the pharmaceutical companies are engaging in this AI space. And none of them, to our knowledge, have thought about implications like this." ■